APPENDIX 2

APPENDIX 2

MANGANESE: ENVIRONMENTAL LEVELS AND POPULATION EXPOSURE

Several commentators have raised questions regarding the impact of HiTEC® 3000 on environmental loadings of manganese. This document summarizes current data on emissions and ambient concentrations of manganese, and analyzes how manganese emissions associated with use of the Additive will impact existing concentrations in the air and soil.

1. Existing environmental loadings of manganese

As the twelfth most abundant element on earth, manganese is naturally present in both air and water. Manganese in the natural environment occurs in a variety of forms, depending on conditions such as soil pH and microbial action. See Final Health Assessment Document for Manganese, Docket No. II-A-3, at 3-56 to 3-60 (1984) ("HAD"). For example, the most common forms of manganese in soil are oxides and hydroxides, of oxidation states +2, +3, and +4, and manganese carbonate. Id. at 3-51. Chemical forms of manganese in solution are even more complex, and can be present in II, III, IV, VI, and VII oxidation states. Id. at 3-56. According to certain researchers, the dominant forms of manganese in sea water include MnO_2 and/or Mn_3O_4. Id. at 3-57.

Since manganese is such an abundant element, people are exposed to it in its various forms every day in air, food, and water. Each of these environmental media are discussed below.

a. Ambient Air

The literature contains both ambient measurement data and estimates regarding the concentrations of manganese in the air. For example, in the United States, background concentrations at rural sites unaffected by major point sources ranged from 0.005 to 0.012 ug/m^3 on an annual basis between 1972 and 1982. HAD at 3-68. Manganese concentrations at these rural sites are principally due to naturally occurring manganese, such as wind-blown dust.

Total emissions of manganese each year from natural sources are estimated to be about 6.1 x 10^{11} grams.[1/] If one apportions these emissions according to land mass, natural emissions of manganese in the United States would be about 3.7 x 10^7 kilograms, or 81 million pounds per year.[2/]

The other principal source of manganese in the ambient air is point source emissions. For example, according to the 1987 SARA Title III emission inventory, point sources emitted a total of 2,740,801 pounds of manganese in that year.[3/] Point sources in Indiana alone emitted about 904,200 pounds of manganese in that year. This SARA Title III information does not include data on emissions from other point sources (e.g., industrial and

---

1/ Galloway, J.N., Thorton, J.D., Norton, S.A., Volchak, H.L. and McLean, R.A.N., "Trace Metals in Atmospheric Deposition: A Review and Assessment," Atmos. Env., 16, 1677-1700 (1982).

2/ The United States has about 6.1 percent of the earth's total land mass.

3/ Toxic Chemical Release Data Base, National Library of Medicine, POXNETT System, 1987 SARA Title III Data.

utility boilers), where manganese is released in trace amounts as a result of the combustion process.

Mobile sources have been a contributor to manganese in the ambient air since the Additive was originally used in leaded gasoline at a concentration up to 0.125 grams per gallon over two decades ago. This Additive was also used in unleaded gasoline for a brief period in the 1970s. Overall, use of the Additive in gasoline peaked in 1985, when about 7,467,000 pounds were produced for U.S. consumption. Assuming 30 percent of the manganese in the Additive was emitted, mobile source emissions of manganese would have been about 546,000 pounds in that year[4/] -- i.e., far less than manganese emissions from both natural and point sources.[5/]

Actual measured concentrations of manganese in urban areas provide some perspective regarding the impact of anthropogenic emissions of manganese on ambient air. For example, the U.S. National Air Surveillance Network reports average ambient

---

[4/] To obtain total manganese emissions, the following calculation applies:

> 7,467,000 pounds of the Additive produced in 1985 for use in the United States x 0.244% (manganese metal in the Additive) x 0.30 (percentage of manganese exhausted as airborne particulate from pre-catalytic vehicles) = 546,584 pounds manganese.

A discussion of manganese emissions from pre-catalytic vehicles is provided in G.L. Ter Haar, et al. "Methylcyclopentadienyl Manganese Tricarbonyl as an Antiknock: Composition and Fate of Manganese Exhaust Products," J. Air Pollution Control, 25 (1975) 858-860 [hereinafter "Manganese Exhaust Products"].

[5/] These mobile source emissions occur as Mn_3O_4, with traces of Mn_2O_3 and MnO. See Manganese Exhaust Products, supra note 4.

concentrations of manganese in urban areas in the United States of up to 0.1 ug/m^3 during the 1950s, and decreasing to 0.03 to 0.05 ug/m^3 during the 1970s and 1980s, the period in which the Additive has been used.[6/] Similarly, ambient concentrations in urban areas of Canada, such as Toronto, are in the 0.04 ug/m^3 range,[7/] even though the Additive has been used in all unleaded gasoline in Canada at a concentration of up to 0.0625 grams per gallon for nearly a decade. In the United Kingdom, where the Additive has never been used, urban ambient concentrations of manganese also have averaged approximately 0.04 ug/m^3.[8/]

Ambient manganese concentrations are also reported in an air quality study examining manganese concentrations in the air at urban sites in California in 1985-87, after refiners began to use the Additive in leaded fuel in California at a concentration of up to 0.1 grams of manganese per gallon.[9/] These sites are influenced by a heavy concentration of automobile emissions. Even so, ambient manganese concentrations were only in the range

---

6/ See 1970-1989 Lead and Manganese Quick Look Reports, Natural Air Data Branch, U.S. EPA, Research Triangle Park, North Carolina; HAD at 3-60 to 3-69.

7/ Air Quality Monitoring Reports for 1982-88, Ontario Ministry of the Environment.

8/ See G. McInnes, Multi-Element and Sulphate in Particulate Surveys: Summary and Analysis of Five Years Results (1976-1981), Warren Springs Laboratory.

9/ See D.W. Davis, et al., "Origins of Manganese in Air Particulates in California," Jour. of Air Pollut. Cont. Assoc. (1988); R.L. Roberson, et al. "Impact of HiTEC 3000 on Ambient Air Manganese Concentrations and Population Exposure and Dose," attached hereto as Attachment 1, at 1-3.

of 0.015-0.03 ug/m^3, and only 0.003-0.013 ug/m^3 of these manganese concentrations were conservatively attributed to mobile sources.[10/]

Finally, it should be noted that manganese in the air behaves as a particulate, and is deposited fairly quickly as a result of normal atmospheric processes. For example, the deposition velocity of vehicle emitted particles from ambient air is estimated to be about 0.26 cm/sec, a level that would lead to deposition of about 20 percent of a given amount of manganese emissions daily.[11/] As a result, and because of the generally low level of anthropogenic emissions of manganese, ambient manganese concentrations in the United States have remained relatively stable in the 0.02-0.05 ug/m^3 range during the 1970s and 1980s. See HAD at 3-60 to 3-69.

This review of data on manganese emissions and ambient concentrations suggests several conclusions. First, most of the manganese present in the ambient air is present as a result of natural causes. Second, maximum reported ambient concentrations of manganese have declined over time, with the application of particulate control technologies to point sources. Third, based on actual monitoring data, ambient concentrations of manganese in

---

10/ Davis, "Origins of Manganese;" supra note 9.

11/ Friedlander, et al., "A New Method for Estimating Dry Deposition Velocities for Atmospheric Aerosols," 1986 J. Aerosol Sci., Vol. 17, No. 3, at 240-44, cited in Attachment 1, at 5; See also HAD at 3-54 to 3-55.

urban areas appear to have remained in the same general range regardless of mobile source contributions.

b. Soil and Water

Since manganese is the twelfth most prevalent element on earth, it is naturally present in a variety of chemical forms in both soil and water. See HAD at 3-51 to 3-57. For example, manganese concentrations in soil range up to about 7,000 ppm, and average about 1,000 ppm. As a result, one cubic meter of soil will contain, on average, approximately one kg of manganese.

Manganese in drinking water is generally at or below the welfare-based standard for drinking water of 50 ug/L.[12/] Stated in other terms, if one watered an acre of lawn to the recommended depth of one inch of water, and that water contained 50 ug/L of manganese, one would deposit about 11 pounds of manganese on the soil simply as a result of watering.[13/]

As noted above, manganese appears in soil in a variety of chemical forms. See HAD at 3-51 to 3-60. Moreover, as a result of chemical and biological processes in the soil, manganese may change from one form to another, and will readily disperse in the soil. See id. at 3-56. As one study has observed,

> Manganese oxides that reach the soil are not likely to remain concentrated in the upper few centimeters for any length of time. The pH of the generally moist conditions prevailing in soils will cause mobilization

---

12/ See HAD at 3-76 to 3-83.

13/ Watering an acre of soil at a rate of one inch requires 27,000 gallons of water. Assuming that water contains 50 ug Mn/L, watering at this rate would result in deposition of 5 kg; or about 11 pounds, of manganese.

> of the manganese, which will move to lower levels and ultimately reach the groundwater or surface waters (Costescu and Hutchinson, 1972).[14/]

For this reason, manganese does not accumulate in a single stratum of soil, close to the surface, where it can readily become airborne, or be taken up by plants, or directly ingested. Rather, the small concentrations of manganese in the ambient air are dispersed in soil and water through natural mechanisms, so that typical concentrations of manganese in soil and water change little over time.

For example, assuming a typical ambient air concentration of manganese in an urban area of 0.04 ug/m^3, a typical soil concentration of manganese of 1,000 ppm, and a standard rate for the deposition velocity of particles,[15/] the soil burden of manganese would change by only about 0.002 percent per month. By the time this small amount of manganese reaches the ground water, it will have dispersed to an extent that it is no different from naturally occurring background concentrations.[16/]

2. Contribution of the Additive to Environmental Loadings of Manganese

Based on particulate emission tests performed as part of the Ethyl test program using the Federal Test Procedure, only about 0.5 percent of the manganese in the Additive would be emitted to the environment. This means that a car using fuel containing the

---

[14/] See The Royal Society of Canada, "Lead in Gasoline: Alternatives to Lead in Gasoline," (February 1986), at 7-8.

[15/] See Attachment 1, at 5.

[16/] See id. at 8.

Additive would emit only about 0.06 grams of manganese annually.[17/]

By contrast, based on testing on pre-catalyst cars burning fuel containing the Additive at a concentration of 0.125 grams manganese per gallon, one could conservatively assume that about 30 percent of the manganese in the Additive would be released.[18/] While it is unlikely that as much as 30 percent of the manganese in the Additive would be emitted from newer cars, given increased engine efficiency in combusting particulate matter and the presence of catalytic converters, whether one uses an emission rate of 0.5 percent or 30 percent, manganese emissions associated with use of the Additive would add little to environmental loadings of manganese.

a. Ambient Concentrations

These emissions would cause little change in ambient manganese concentrations. As noted above, manganese concentrations in Toronto, Canada (where the Additive is widely used at up to twice the concentration at issue in this request) are about 0.04 ug/m^3 -- a level identical to those reported in urban areas in the United Kingdom where the Additive is not used. In the United States, urban ambient concentrations during the

---

17/ See Ethyl Waiver Application, Appendix 2.

18/ See Manganese Exhaust Products, supra note 4. This testing was based on an urban driving cycle.

1970s and 1980s have been in the 0.02-0.05 ug/m^3 range, even though the Additive has been widely used in older cars.[19/]

That use of the Additive would have little effect on ambient concentrations is also confirmed by a study of the impact of the Additive on manganese concentrations in Southern California.[20/] This study shows that, even with use of the Additive at a concentration of up to 0.125 grams manganese per gallon in leaded gasoline, urban concentrations of manganese remained in the range of 0.015-0.03 ug/m^3. This study suggests that use of the Additive conservatively contributed only 0.003 to 0.012 ug/m^3 of the manganese in the ambient air in Southern California.[21/]

Finally, these results are confirmed by additional air quality analyses relating concentrations of manganese emissions from mobile sources to concentrations of another pollutant that has been emitted from mobile sources, tetraethyl lead, or TEL. For example, if one applies the ratio of manganese to TEL emitted from mobile sources to typical concentrations of lead in the urban atmosphere after 50 years of use of TEL, the maximum increase in ambient manganese concentrations anticipated with use of the Additive is predicted to be only about 0.017 ug/m3.[22/] If one assumes that only 0.5 percent of the manganese in the

---

19/ See HAD at 3-67.

20/ See Davis, "Origins of Manganese," supra note 9.

21/ See Attachment 1, at 1-2.

22/ See Attachment 2, Table 2.

Additive is emitted, ambient manganese concentrations are predicted to increase by less than 0.001 ug/m3.[23/]

In short, these data and analyses show that the Additive will contribute at most about 0.017 ug/m^3 to ambient concentrations of manganese in the urban environment. That the maximum ambient impact is likely to be smaller is suggested by both the California data and the Canadian experience.

b. Concentrations in Soil and Water

Since manganese emissions resulting from use of the Additive are small, any effects on manganese concentrations in soil or water will also be small. For example, even if one assumes (1) that all manganese emitted will be deposited to the soil, and (2) that this deposition will be concentrated in twenty percent of the land mass of the United States (to reflect concentrations of population and automobile traffic), then the annual deposition rate of manganese will range from less than 0.05g/ha/yr to 3 g/ha/yr (depending on whether one assumes 0.5 percent or 30 percent of the manganese in the Additive is emitted).[24/] For

---

[23/] Id.

[24/] An example of this calculation is as follows, for the 0.5 percent case:

$$19{,}000 \text{ lb} \times .454 \text{ kg/lb} = 8600 \text{ kg Mn/yr}$$

$$\frac{8.6 \times 10^3 \text{ kg Mn/yr}}{1.86 \times 10^8 \text{ ha}} = < 0.05 \text{ g/ha average}$$

urban areas, this would reflect an increase in the current deposition of manganese by about 0.005 to 0.3 percent.[25/]

Another way to look at the potential effect of manganese emissions on soil concentrations is to relate the manganese emissions resulting from use of the Additive to the emissions of lead resulting from use of tetraethyl lead (TEL). For example, (i) assuming that manganese would enter the environment in the same ratio that TEL did; (ii) accounting for the fact that the concentration of manganese in fuel is almost 100 times less than that of TEL, use of the Additive would have an almost imperceptible impact on manganese soil concentrations. Average soil concentrations of manganese only one meter from an expressway carrying 100,000+ cars/day would increase from about 1000 ppm, on average, to only 1000.1 ppm after 50 years of use of the Additive. In fact, even if one assumed that 30 percent of the manganese used in the Additive was emitted, manganese soil concentrations one meter from the expressway would increase,

---

[25/] The annual deposition of manganese in the United States has been reported as follows:

Location	Mn Deposited (g/ha/yr)	Type	Year
Rural	< 310	wet	1979
	< 250	dry	1979
	< 290	bulk	1979
	< 21	bulk	1976
	< 250	bulk	1977
Urban	< 830	dry	1979
	< 990	wet	1979
	< 1000	bulk	1979

Galloway, et al., supra note 1.

after 50 years of use, from 1000 ppm, on average, to only 1012 ppm.[26/] As the distance from the expressway increases beyond one meter, the Additive's contribution to manganese in soil decreases exponentially, totally disappearing as a practical matter at a distance beyond 15 meters.[27/]

To evaluate yet further the potential contribution of manganese emissions resulting from use of the Additive to soil concentrations, Ethyl requested that SAI, Inc. undertake a modeling analysis.[28/] Based on values reported in the literature and conservative assumptions regarding (i) the contribution of the Additive to ambient concentrations, (ii) the deposition rate of manganese, (ii) the mixing depth in soil, and (iv) background concentrations, SAI concludes that "even in 70 years, and even ignoring losses to the subsoil and ground water, the increment to the crustal burden would not be distinguishable."[29/]

Finally, since so little manganese will be deposited in soil, concentrations of manganese in water will not change appreciably. Dispersion of the small amounts of manganese emissions at issue in soil and water will have an effect far less than normal variations in background concentrations.[30/]

[26/] See Attachment 2, Table 1.

[27/] See id.

[28/] See Attachment 1.

[29/] Id. at 7.

[30/] See id. at 7-8.

3. Population Exposure

Since manganese emissions associated with use of the Additive will have little effect on environmental loadings of manganese, use of the Additive will not change, as a practical matter, environmental exposures to manganese. For example, typical daily intake of manganese from food and water ranges from 2,000-9,000 ug, and averages about 3,000 ug.[31/] (The daily intake from inhalation in an urban area (assuming an ambient concentration of 0.04 ug/m^3 and a normal daily breathing rate of 20 m^3) would be about 0.8 ug.[32/] Assuming an absorption rate of 4 percent from ingestion and 25-50 percent from inhalation,[33/] about 120 ug will be absorbed each day, with a typical range of from 80-360 ug.

In other words, the typical amount of manganese absorbed each day from food, water, and air can vary up to 7,000 ug. This amount of variation in normal manganese intake and absorption is understandable when one examines the variation in manganese concentrations in typical foods. Some examples are given below:[34/]

Grains	
1 slice whole wheat bread	334 ug
1 slice white bread	164 ug

31/ See Waiver Application, Appendix 8.

32/ See id.

33/ See HAD at 4-3.

34/ Guthrie, B. E., Chromium, Manganese, Copper, Zinc and Cadmium Content of New Zealand Foods, New Zealand Med. J., Dec. 24, 1975, 418-424.

Fruits	
1 Granny Smith Apple	45 ug
1 Banana	255 ug
1 Bosc Pear	7.5 ug
1 Paterson Late Plum	72 ug
Vegetables	
3 oz Kidney Beans	987 ug
3 oz Asparagus	70 ug

Moreover, according to SAI, since use of the Additive would not contribute to soil concentrations distinguishable from manganese already in soil,[35/] there would be no appreciable increase in public exposure from the ingestion pathway. In addition, based on total manganese dose to an individual as the sum of ingestion and inhalation dose, and accounting for 70 years of manganese buildup based on conservative assumptions regarding mobile source contribution to ambient manganese,[36/] SAI has concluded that conservatively estimated doses from all pathways "are totally insignificant" -- less than one-tenth of one percent of the typical daily intake of manganese. As a result, SAI concludes that exposure to manganese emissions that results from

---

[35/] See Attachment 1, at 7.

[36/] Significantly, the SAI analysis and the conclusions drawn in that analysis are not affected by the assumptions one might make regarding the percentage of manganese in the Additive that is emitted from the tailpipe. This is so because SAI based its analysis on typical urban concentrations of manganese, and conservative assumptions as to the amount of manganese in the urban air attributable to mobile source traffic. This latter assumption was based on the most conservative ratio (i.e., 0.43) found in Davis, et al., supra note 9.

use of the Additive will be insignificant and indistinguishable from normal exposure to manganese in the environment.[37/]

For all of these reasons, use of the Additive will not, as a practical matter, change the exposure of people to manganese.

Attachments (2)

37/ See id. at 37.

Attachment 1

-- TECHNICAL NOTE --

IMPACT OF HiTEC 3000 ON AMBIENT AIR MANGANESE CONCENTRATIONS AND POPULATION EXPOSURE AND DOSE

July 1990

Prepared for
Ethyl Corporation
Richmond, Virginia

Prepared by
Ralph L. Roberson, P.E.
Roberson Pitts, Inc.
Raleigh, North Carolina
and
Gerald E. Anderson, Ph.D.
Systems Applications, Inc.
San Rafael, California

Report No. 90-220-04F

IMPACT OF HiTEC 3000 ON AMBIENT MANGANESE CONCENTRATIONS

AMBIENT AIR CONCENTRATIONS

Special Studies

Davis, et al.[1] studied ambient concentrations in California during 1985 to 1987. Samples of total airborne particles at 20 sites in California were collected using low-volume samplers. Samples of fine and coarse particles at five sites were collected with dichotomous samplers. Each sample was collected over a 24-hour period of time. It was during this time period that oil refiners added an anti-knock compound containing manganese to leaded gasoline. Davis, et al. reported the following average Mn concentrations:

Central Valleys (e.g., Bakersfield, Fresno, Modesto, Stockton, etc.)	30 ng/m^3
Bay Area (e.g., Concord, Fremont, Richmond, San Francisco, San Jose, etc.)	15 ng/m^3
Southern California (e.g., Long Beach, Los Angeles, Rubidoux, Santa Barbara, etc.)	30 ng/m^3

In another study, Pierson, et al.[2] examined manganese concentrations at two tunnels on the Pennsylvania Turnpike. Measurements were made for the Allegheny Tunnel in July 1975 and May 1976 and for the Tuscarora Tunnel in August 1976 and June 1977. By the time of the August 1976 measurements, MMT had started to appear on the market. From August 1976 to July 1977, the use of MMT in unleaded gasoline sold at Turnpike service plazas increased, as did the unleaded share of total gasoline sales at the plazas, giving a 4-fold increase in overall average Mn concentration (from 4 mg/gal to 16 mg/gal) in gasoline between the two dates. For the August 1976 and July 1977 sampling

periods, Pierson, et al. attributed an increase in manganese concentrations, due to mobile source emissions, ranging from 70 to 110 ng/m^3. Attribution of manganese was determined by subtracting manganese concentrations determined in "outside" tunnel air from manganese concentrations measured in the tunnel. Finally, based on the average Mn/Pb emission rate ratio from automobiles in 1977, Pierson, et al. estimate an ultimate vehicle-derived manganese level in ambient air of approximately 20 ng/m^3. This estimate is based on MMT use in all gasolines and at a rate of 1/16 g Mn/gal. Pierson, et al. state that the 20 ng/m^3 concentration is overstated if MMT levels are below 1/16 g Mn/gal. Of course, Ethyl's wavier application is based on a usage rate of only 1/32 g Mn/gal.

Historical Data

It is interesting to compare the results of the above-discussed special studies with typical manganese concentrations reported in the literature. For example, EPA reports average manganese concentrations for U.S. urban areas to be 38 ng/m^3; average concentrations for non-urban areas are reported to be 9 ng/m^3.[3] Davis, et al. purportedly found an effect of MMT on ambient manganese concentrations in California; however, the EPA data clearly show that manganese concentrations in typical urban areas is greater than the total manganese concentrations reported by Pierson, et al.

Ambient air quality data from Canada also support the claim that MMT does not measurably contribute to ambient concentrations of manganese. MMT has been used in virtually all unleaded gasoline in Canada for well over a decade at concentrations up to 1/16 g Mn/gal. Ambient monitoring data from Ontario's extensive sampling network is summarized below.[4]

	Manganese Concentations (ng/m^3)	
	Urban	Non-Urban
Excluding Cities with Point Sources	34	19
Including Cities with Point Sources	70	--

These data indicate that ambient manganese concentrations are strongly dependent on the presence of point sources. Also, in the absence of point sources, ambient manganese concentrations in urban areas where automobiles burn gasoline containing MMT compare favorably with typical U.S. manganese concentrations (i.e., 34 ng/m^3 versus 38 ng/m^3). These ambient manganese concentrations are consistent with urban manganese concentrations for the United Kingdom (i.e., 40 ng/m^3) -- where MMT has never been used in gasoline.[6]

Summary

The results among special studies and historical data are consistent in predicting the impact of HiTEC 3000 on ambient air manganese concentrations. It is interesting to note that current ambient manganese concentrations appear to be independent of historical use of MMT in fuel (e.g., Canada ≈ 34 ng/m^3, where MMT is widely used; the United Kingdom ≈ 40 ng/m^3, where MMT has never been used; and the United States ≈ 38 ng/m^3).

EXPOSURES AND DOSES

Systems Applications, Inc. (SAI) carried out some simple calculations to estimate the possible human exposure to and doses of manganese that might

result from general use of HiTEC 3000 as a motor fuel additive. Our focus is on exposure through dermal absorption from and ingestion of contaminated soil; although we calculate a coincident inhalation dose for comparison and completeness. Results show that by any reasonable criterion, any such exposures would be totally insignificant.

The approach taken is to use published data, where possible, to calculate long-term increments to the naturally occurring manganese burden of soil and then to use regulatory guidance for parameters to estimate the dose to the population from soil doses through skin contact and ingestion.

The algorithms and data used, and their sources, are as follows:

- Urban concentrations of ambient atmospheric manganese are found to be 0.034 $\mu g/m^3$ (maximum median concentration in National Air Surveillance Network),[6] 0.05 $\mu g/m^3$ if 0.125 g/gal of MMT were used in all cars,[7] and ranging from 0.015 to 0.04 $\mu g/m^3$ for various urban areas[8] in California and Canada. The largest California value (0.03 $\mu g/m^3$) is used in the present analysis because other data (e.g., fraction attributable to motor vehicles, deposition velocity) are taken from Los Angeles studies.

- The fraction of the ambient manganese attributable to motor vehicle emissions come from Davis, et al. (also Table 1). The fraction for Los Angeles is measured to be 0.43. This is much higher than the fraction, 0.19, found for the San Francisco Bay Region; therefore, the larger value is used.

- The deposition velocity of vehicle-generated particles from ambient air is estimated by Friedlander, Turner, and Hering to be 0.26 cm/sec.[9] This value is based on the relative (measured) ambient concentrations of lead and CO at source locations and at (downwind) receptor locations. Both species are known to be highly correlated with motor vehicle emissions in urban atmospheres. Lead is a depositing species and CO is not; thus, decreasing ratios of these concentrations downwind is a measure of the deposition of the lead. The measurements were made in the Los Angeles region for particles in the size range below 1 μm. This is the size range appropriate for motor vehicle-generated manganese also. This empirical determination of deposition velocity is used because it has the virtue that it is based on measurements in an urban environment of interest, with real surface roughness, etc. and of particles characteristic of auto emissions.

- The background concentrations of manganese in soil (1,000 ppm) and in "street dust" (300 ppm) are reported by Joselow, et al.[10] (street dust) and Davis, et al. (for the earth's crust -- op cit, page 1152 -- citing Handbook of Chemistry and Physics). It is assumed, conservatively, that street dust would be removed by rain, sweeping, or resuspension by traffic at least monthly. Precipitation is much more frequent than monthly in many Los Angeles months and in all months in other climatic regions.

- The depth to which fine particles may be considered mixed in soil upon which they are deposited is given as 1 centimeter in the proposed

toxic regulations by the SCAQMD (Los Angeles).[11] Actual depths may be much greater due to leeching or agricultural tillage. For street dust we assumed a depth of 1 millimeter.

- The soil ingestion rate for all age groups recommended by the SCAQMD (op cit, page B-9, citing the California Dept. of Health Services) for use in risk analysis is close to 150 mg/day. An absorption factor for Mn for the GI tract is assumed as 4 percent, based on studies by Mena, et al.[12]

- The dermal dose of soil recommended by the SCAQMD[13] for use in risk analysis is 400 mg/day, with an absorption of from 1 percent (inorganics) to 10 percent (organics). Since we are examining an inorganic form of the manganese in the soil, we use the 1 percent absorption rate.

- The ventilation rate recommended by the SCAQMD[14] for use in risk analysis is 20 m^3/day.

- The algorithm for manganese deposited on street or soil is based on proportionality to the ambient concentration and the deposition velocity. Thus,

  -- Deposition ($g/m^2/s$) = Deposition velocity (m/s) x concentration ($\mu g/m^3$).

  -- Mn Deposition ($g/m^2/s$) = Deposition ($g/m^2/s$) x fraction of ambient from motor vehicle.

- The fractional deposition increment, per year, of motor vehicle related manganese is the annual deposition (g/m^2) divided by the soil burden, where the soil burden is

-- Soil burden (g/m^2) = Soil concentration ($\mu g/m^3$) x mixing depth (m).

Fractional deposition is calculated for "street dust" and for soil ("crustal" material). The results are as follows:

-- Street dust: 0.0221 percent/month (assuming that street dust is "fresh" on a monthly basis).

-- Crustal: 0.0080 percent/year.

No accumulation of manganese in street dust is assumed beyond the 1 month replacement period. Crustal material is conservatively assumed to be incremented indefinitely in the 1 centimeter mixing depth. In 70 years, the increment to the "natural" value would be:

70 (yr) x 0.0080 (%/yr) = 0.56 percent.

Thus, even in 70 years, ignoring losses to the subsoil and ground water, the increment to the crustal burden would not be distinguishable.

Human doses are computed for dermal, ingestion, and inhalation routes of exposure. These results are compared to an average daily dietary uptake of manganese of 0.120 mg/day.

- Dermal

  Dose (mg/day) = (Soil contact)(mg/day) x (fraction Mn) x (fraction absorbed).
  Street = (400)(300 ppm ÷ 10^6)(0.000221)(0.01)
  Street = 2.65 x 10^{-7} mg/day.
  Crustal = 2.24 x 10^{-5} mg/day.

- Ingestion

  Dose (mg/day) = (Soil ingestion)(mg/day) x (fraction Mn) x (fraction absorbed).
  Street = (150)(300 ppm ÷ 10^6)(0.000221)(0.04)
  Street = 0.4 x 10^{-6} mg/day.
  Crustal = 3.3 x 10^{-5} mg/day.

- Inhalation

Dose (mg/day) = Concentration ($\mu g/m^3$) x ventilation rate (m^3/day)
= (0.03 $\mu g/m^3$)(1 mg/1,000 μg)(20 m^3/day)
= 6.0×10^{-4} mg/day.

The total manganese dose to an individual is estimated as the sum of dermal, ingestion, and inhalation dose. Separate results are calculated for soil dose from street or crustal material. We choose not to combine these exposure doses to give population exposure profiles; these separate estimates may be interpreted as corresponding to persons being exposed to manganese from street or crustal material. Results are:

-- Street: 6.01×10^{-4} mg/day = 0.50 percent of 0.120 mg average daily dietary uptake

-- Crustal: 6.55×10^{-4} mg/day = 0.55 percent of 0.120 mg average daily dietary uptake.

Since normal dietary intake varies on the order of milligrams per day, these submicrogram doses are totally insignificant.

Doses through groundwater are expected to be even less significant. Untreated ground water is not drawn for domestic consumption from closer than a few meters (as much as hundreds of meters) from the surface. Thus, any manganese migrating to such depths would be diluted by factors of from several hundred to several tens of thousands by admixture with a crustal volume much deeper than the one centimeter assumed here.

We repeat the above dose calculations in terms of manganese intake instead of manganese uptake.

- Ingestion

  Dose (mg/day) = (Soil ingestion)(mg/day) x (fraction Mn)
  Street = (150)(300 ppm ÷ 10^6)(0.000221)
  Street = 1.0×10^{-5} mg/day.
  Crustal = 8.25×10^{-4} mg/day.

- Inhalation

  Dose (mg/day) = Concentration ($\mu g/m^3$) x ventilation rate (m^3/day)
  = (0.03 $\mu g/m^3$)(1 mg/1,000 μg)(20 m^3/day)
  = 6.0×10^{-4} mg/day.

Total manganese intake is reported as the sum of ingestion and inhalation exposure, and compared to an average daily intake value of 3 mg/day.

-- Street: 6.10×10^{-4} mg/day = 0.02 percent of 3 mg average daily intake

-- Crustal: 1.43×10^{-3} mg/day = 0.05 percent of 3 mg average daily intake.

REFERENCES

1. D.W. Davis, K. Hsiao, R. Ingel, and J. Shikiya, "Origins of Manganese in Air Particulates in California," J. Air Pollut. Control Assoc. 38:1152 (1988).

2. W.R. Pierson, D.E. McKee, W.W. Brachaczek, and J.W. Butler, "Methylcyclopentadienyl Manganese Tricarbonyl: Effect of Manganese Emissions from Vehicles on the Road," J. Air Pollut. Control Assoc. 28:692 (1978).

3. Environmental Protection Agency, "Health Assessment Document for Manganese" (1984).

4. Ontario Ministry of Environment, "Air Quality Monitoring Report 1982-87."

5. G. McInnes, "Multi-Element and Sulphate in Particulate Surveys: Summary and Analysis of Five Year Results (1976-1981), Warren Springs Laboratory Report LR435(AP), 1982.

6. Potential Health Effects of Manganese in Emission from Trap-Equipped Diesel Vehicles. Page 8, Sept. 1988, Health Effects Institute, Cambridge, MA.

7. Ibid, page 27, citing Ter Haar.

8. Davis, et al., pages 240-244.

9. S. Friedlander, Turney and Hering. "A New Method for Estimating Dry Deposition Velocities for Atmospheric Aerosols." J. Aerosol Sci., 17:3, pp 240-244. Pergammon Jnls. Ltd. (1986).

10. Joselow, Morris M., E. Tobias, R. Koehler, S. Coleman, J. Bogden, and D. Gause, "Manganese Pollution in the City Environment and its Relationship to Traffic Density," AJPH, Vol.68, No.6, June 78. p 558.

11. South Coast Air Quality Management District, Planning Division Staff Report, Proposed Rule 1401, New Source Review of Carcinogenic Air Contaminants. April 1990, p B-7.

12. I. Mena, K. Horiuchi, K. Burke, and G.C. Cotzias. 1969. Neurology, Vol. 19, pp 1000-1006.

13. Table 4-7; Multi-pathway Health Risk Assessment Input Parameters Guidance Document. Prepared for SCAQMD by Clement Associates, Inc., Fairfax, VA; Feb. 1988.

14. Ibid.

ATTACHMENT 2

Environmental Impact of MMT Usage

One method of predicting the environmental impact of the manganese emissions resulting from use of the HiTEC 3000 Performance Additive (the "Additive") is to relate the manganese emissions to emissions of lead from prior use of Tetraethyl Lead (TEL). Assuming that manganese would enter the environment in the same ratios as lead did, there will be only a minimal environmental impact resulting from use of the Additive. The concentration of TEL in gasoline averaged about 2.5 g/gal. during fifty years of use.

It should be noted that the maximum environmental levels predicted from this model do not depend on knowledge of the exact percentage of either manganese or lead emitted. The model assumes only that similar percentages are emitted. This is an extremely conservative assumption due to changes in automotive design that have been implemented since the introduction of unleaded gasoline such as electornic fuel injection, oxygen sensors and catalytic converters.

Soil along the busiest expressways may contain elevated levels of lead which decline exponentially with distance from the road. At about 50 meters from the road, background levels are present. Not all the lead in soil resulted from TEL usage, but to make the model give the worst case, the calculations are based on the assumption that all the increase in soil lead resulted from TEL usage. Because HITEC 3000 is to be used at 0.03125 g/gal, the amount of manganese going into the environment would be 0.03125 g Mn/gal/2.5 g Pb/gal or only 0.0125 times as much.

The impact of HiTEC 3000 use on soil manganese levels based on the lead experience is shown in Table 1. Table 1 shows that even if 30 percent of the manganese in the additive was emitted <u>over 50 years of use</u>, the increase in levels of manganese in soil would be very small, even within 1 meter of a busy expressway. The additional manganese would be less than an amount well within the natural variation in soil[1].

---

[1]HAD 3-27

As the estimated amount of manganese emitted from the tailpipe diminishes, the relative impact on manganese in soil concentrations becomes almost imperceptible. For example, assuming 0.5 percent of the manganese in the Additive is emitted (a level consistent with particulate testing completed by Ethyl on several test cars),[2] the increase in manganese in the soil after 50 years of use one meter from the expressway is only 0.1 ppm.

Of note, manganese is mobile in soil. Microorganisms in soil cause the manganese to undergo valence changes which result in solubilization. Some have suggested that manganese passes freely into solution in acid, water-logged soils and is circulated in groundwater. Upon entering streams with average pH biological oxidation potential, manganese is precipitated. Much of it eventually enters the ocean; however, there is no evidence that levels of manganese in ocean water have increased as a result of anthropogenic activities. See HAD 3-56-3-59 for discussion. For this reason, the manganese levels reflected in Table I reflect worst-case conditions.

---

[2] See Waiver Application, Appendix 3.

One can also predict the impact of HiTEC 3000 on manganese in air levels, based on the experience with TEL. About 89.4% of airborne lead came from automotive sources[2] . Urban air lead levels for the period were about 1-3 ug/m^3 and non-urban levels were about 0.1-0.5 ug/m^3[3]. The average was about 1.5 ug/m^3 for urban levels. Then TEL contributed 1.5 x 89.4% or 1.34 ug/m^3 in urban areas. Multiplying by the ratio of manganese to lead, 0.0125, gives the predicted increase in airborne manganese. Table 2 shows predicted changes in airborne manganese levels under three manganese emission assumptions: (1) 30 percent of the manganese in the Additive emitted; (2) 5 percent of the manganese emitted; and (3) 0.5 percent of the manganese emitted. The maximum increase in ambient manganese would be only 0.017 ug/m^3 for urban areas. Levels in urban areas are presently about 0.038 ug/m^3[4].

These amounts are quite low. The average adult inhales about 20 m^3 of air/day. Therefore, the average increase in exposure in urban areas would be predicted to be 0.33 ug/day compared to dietary intakes averaging about 3 mg/day. This is approximately 10,000 times more than the increase in intake from the air under worst-case assumptions with HiTEC 3000 usage. These increases are also well within the normal variation due to difference in climatic and geological conditions and anthropogenic activities.

---

[2]Air Quality Criteria for Lead, EPA/600/8-83/0286F p. 5-8, 1986.

[3]Lead; Airborne Lead in Perspective, National Acadamy of Sciences, Washington, D.C., 1972, p. 21.

[4]HAD

As with manganese in soil concentrations, the estimated impact of manganese emissions resulting from use of the Additive diminishes substantially as the estimated amount of manganese emitted from the tailpipe diminishes. Assuming that only 0.5 percent of the manganese in the Additive is emitted[5], for example, the increase in ambient concentrations of manganese is predicted to be less than 0.001 ug/m^3 for a typical urban area.

031GDP90

---

[5]See Waiver Application, Appendix 3.

TABLE 1

Impact of HiTEC Usage on Soil Manganese Levels after 50 Years of Use
Calculations Based on Expressway Carry 100,000+ Cars/Day

Distance From Road	Natural Mn in Soil		Contribution from HiTEC[1]		Total Predicted Level
1 meter	1000	+	12.3	=	1012.3
5 meters	1000	+	4.6	=	1004.6
15 meters	1000	+	2.6	=	1002.6
5% of Mn Emitted[2]					
1 meter	1000	+	2.2	=	1002.2
0.5% of Mn Emitted[2,3]					
1 meter	1000	+	0.22	=	1000.2

1. Based on a hypothetical case where lead in soil might be as high as 1000 ppm, 368 ppm and 208 ppm at 1,5 and 15 meters from the expressway and a natural background of 15 ppm. The level above background was multiplied by 0.0125 to arrive at the HiTEC contribution.

2. Based on an assumption that 30% of the lead was emitted.

3. Based on actual testing - see Waiver Application, appendix 3.

031GDP90

TABLE 2

Predicted Changes in Airborne Manganese Levels

Location

URBAN (Air Pb value of 1.5 ug/m^3 x 90% or 1.35 ug/m^3 from TEL)

1.35 ug Pb/m^3 x 0.0125 Mn/Pb = 0.017 ug Mn/m^3

At 5% of Mn emitted[1]

1.35 ug Pb/m^3 x 0.0021 Mn/Pb = 0.003 ug Mn/m^3

At 0.5% of Mn emitted[1,2]

1.35 ug Pb/m^3 x 0.00021 Mn/Pb = < 0.001 ug Mn/m^3

1. Based on an assumption that 30% of the lead was emitted.

2. Based on actual testing - see Waiver Application, appendix 3.

031GDP90

APPENDIX 3

ANALYSIS OF HEALTH RISK FROM THE ADDITION OF HITEC-3000 TO UNLEADED GASOLINE AT A CONCENTRATION OF 0.03125 GRAMS OF MANGANESE PER GALLON OF GASOLINE

Prepared by

H. Daniel Roth, Ph.D.
Philip A. Walker, M.S.
Roth Associates, Inc.
6115 Executive Boulevard
Rockville, Maryland 20852

Prepared for

Hunton & Williams
2000 Pennsylvania Avenue, NW
Washington, DC 2036

July 1990

TABLE OF CONTENTS

LIST OF ATTACHMENTS

A-1 Curriculum vitae for Drs. Higgins, Landau, Roth, and Schulz, and Mr. Walker

A-2 Letter from Dr. Carl O. Schulz to Dr. Neil Roth

B-1 United States Environmental Protection Agency, *Health Assessment Document for Manganese* (August 1984)

B-2 Health Effects Institute, *Potential Health Effects of Manganese in Emissions from Trap-Equipped Diesel Vehicles: A Report from the Health Effects Institute* (September 1988)

B-3 Letter from Hershel E. Griffin, M.D. and Norton Nelson, Ph.D. to the Hon. William D. Ruckelshaus

C-1 Sky-Peck (1990)

C-2 Landau, Review of: *Manganese, a Physiological Marker for Criminal Violence* by Gottschalk et al.

C-3 Higgins, Comments on: *Manganese, a Physiological Marker for Criminal Violence* by Gottschalk et al.

C-4 Stauber and Florence (1989)

C-5 Hams and Fabri (1988)

C-6 Cawte et al. (1989)

C-7 Landau, Review of: *Epidemiological Survey Among Workers Exposed to Manganese: Effects of Lung, Central Nervous System, and Some Biological Indices* by Roels et al.

C-8 Wang et al. (1989)

C-9 Huang et al. (1989)

C-10 Phoon (1988)

C-11 Nogawa et al. (1973)

C-12 Landau, Review of: *Studies of the Effects on the Respiratory Organs of Air Pollution Consisting of Dusts Composed Mainly of Manganese. (First Report). Effects*

on the Respiratory Organs of Junior High School Students by Nogawa et al. (1973)

C-13 Higgins, Comments on: *Studies of the Effect on Respiratory Organs of Air Pollution Composed Mainly of Manganese (First Report) Effects on the Respiratory Organs* by Nogawa et al. (1973)

C-14 Bleecker (1988)

C-15 Donaldson (1987)

C-16 Abbott (1987)

C-17 Cooper (1984)

D-1 Schulz, *A Review of the Memorandum Entitled, "Manganese in Gasoline, Toxicity Problems" by the Director, NIEHS dated June 7, 1990*

D-2 Schulz, *Contrasting Public Health Concerns Raised by Lead, Manganese, and MMT*

D-3 Schulz, *A Brief Comment on "Manganese and Human Health" by John Donaldson in Manganese in the Canadian Environment by the National Research Council Canada, 1988*

D-4 Schulz, *Review of Testimony by Ellen Silbergeld*

EXECUTIVE SUMMARY

The Ethyl Corporation has applied for a waiver for the gasoline additive methylcyclopentadienyl manganese tricarbonyl (MMT) pursuant to § 211(f)(4) of the Clean Air Act. If the waiver is granted, MMT could be added to unleaded gasoline at concentrations up to 0.03125 grams of manganese per gallon of gasoline. Ethyl Corporation has advised us that for a typical large urban area, the best estimate of the maximum increased ambient concentration of manganese as a result of such addition is 0.0009 $\mu g/m^3$. To be conservative, we have also considered the possibility of ambient manganese contributions as high as 0.09 $\mu g/m^3$.

Health Studies of Manganese: In this report, we have examined the toxicological and epidemiological literature on manganese in order to evaluate the likely health impact of widespread use of MMT as a fuel additive. In performing this task, we took advantage of earlier assessments of the manganese health effects data including an EPA Health Assessment Document in 1984, a World Health Organization (WHO) review in 1981, and a Health Effects Institute (HEI) review that was completed in 1988. The HEI report is of particular significance because it addressed the issue of manganese being used as a fuel additive. In this report, we summarized findings from EPA's 1984 Health Assessment Document on manganese and from the 1988 HEI Report. We also examined key health studies of manganese published since the 1988 HEI Report.

We have found that the use of MMT is unlikely to affect public health adversely. The anticipated increase of manganese in the environment from use of MMT is sufficiently small in comparison to the natural levels of this element and human intake of it that the body's ability to maintain consistent manganese levels should be unaffected. Thus, no effect on health would be anticipated. Data concerning the impact of exposure to such small amounts of manganese is limited, but it is consistent with the lack of any effect.

Issues Raised by Commenters: At least five commenters have expressed concerns that even small amounts of manganese emissions related to MMT usage might pose a significant health threat. These commenters include the National Institute of Environmental Health Sciences (NIEHS), the Environmental Defense Fund (EDF), Mr. Everett L. Hodges, Dr. John Donaldson, and Dr. Herbert L. Needleman.

The comments cover a wide range of alleged health impacts, but they focus primarily on neurological effects. Two specific neurological concerns are that manganese contributes to neurological diseases of aging such as Parkinson's disease and that manganese is associated with a tendency toward violent, criminal behavior. Other specific concerns relate to respiratory and reproductive effects. Finally, there is a general allegation that health concerns about lead as a fuel additive argue against approval of a fuel additive containing manganese because manganese, like lead, is a metal.

We have found none of the above issues to be of concern. First, manganese is very different from lead chemically, biologically, and environmentally. Thus, the experience with lead as a gasoline additive cannot be used as a model of what will happen if MMT is added to gasoline. Second, while high levels of manganese (i.e. >300 $\mu g/m^3$) are associated with neurological effects, concern that exposure to the far lower manganese levels expected to results from MMT use has no basis. Finally, the concern that manganese is associated with violent criminal behavior is essentially speculation. The one study that directly supports it is seriously flawed. Similarly, none of the other concerns raised by commenters provides a sound basis for concluding that the addition of MMT to gasoline as proposed by Ethyl would endanger public health.

Benefits of Pollutant Reduction: In addition to evaluating the health literature on manganese, we have qualitatively examined the benefits which would result from using the Ethyl fuel additive. Ethyl has demonstrated that the use of their product would substantially reduce emissions of CO, NO_x, and aromatic hydrocarbons. Some of these substances have been shown to be

closely associated with respiratory conditions, while others are known carcinogens. Thus, the benefits derived from reducing their emissions can be substantial.

Summary: In summary, examination of the epidemiological and toxicological data indicates that exposure to manganese at levels that would result from using MMT as a fuel additive will not pose a health threat. The available epidemiological data indicate that manganese has neurotoxic and, perhaps, respiratory effects only at levels many times higher than those related to MMT usage. This conclusion is similar to that of the 1988 HEI report which found that manganese would be safe as a diesel fuel additive. In fact, use of MMT would lead to reductions in emissions of other compounds of health concern at or near ambient levels. Thus, the net result of MMT use is likely to be a reduction in health risk.

A. INTRODUCTION

The Ethyl Corporation has applied for a waiver for the gasoline additive methylcyclopentadienyl manganese tricarbonyl (MMT) pursuant to § 211(f)(4) of the Clean Air Act. If the waiver is granted, MMT could be added to unleaded gasoline at concentrations up to 0.03125 grams of manganese per gallon of gasoline. Ethyl Corporation has advised us that its analyses indicate that, for a typical large urban area, the best estimate of the maximum increased ambient concentration of manganese as a result of such addition is 0.0009 $\mu g/m^3$. We were advised, however, to consider the possibility of ambient manganese contributions as high as 0.09 $\mu g/m^3$ to be conservative.

Issues Raised by Commenters: At least five commenters suggest that even the small manganese emissions related to MMT usage pose a significant threat to public health and they therefore oppose Ethyl's application for a waiver for the additive. First, the National Institute of Environmental Health Sciences (NIEHS) expresses concern about effects of manganese on the central nervous system and draws parallels between lead and manganese in terms of the potential for health effects. In addition, NIEHS indicates that manganese in the form of Mn_3O_4 is more toxic than other salts or oxides of manganese. Finally, NIEHS questions the applicability of existing data on respiratory exposure to the manganese concentrations that would be expected from MMT in gasoline.

Second, the Environmental Defense Fund (EDF) indicates that manganese is a neurotoxin. In addition, EDF indicates that manganese is a "lung toxin." EDF also indicates that manganese may affect the aging brain since it damages the nigrostriatal system. Finally, EDF suggests manganese may cause fetal and early developmental effects.

Third, Mr. Everett L. Hodges and Dr. John Donaldson express concern that excessive manganese is found in the hair of "violent individuals." They also hypothesize that chronic exposure to low levels of manganese may contribute to premature senescence of

neurons in the substantia nigra region of the brain. A paper prepared by Dr. Donaldson for the Canadian National Research Council and submitted to the docket by Mr. Hodges also suggests that manganese may adversely affect human reproduction, cellular glucose metabolism and the antibacterial action of white blood cells.

Finally, Dr. Herbert L. Needleman, also drawing an analogy to lead, states that MMT is a neurotoxin. He indicates that manganese exposure is related to Parkinson's disease and affects control of movement.

Scope of Review and Findings: This report examines the basis for the above comments and evaluates the possible public health impact of the manganese emissions that would result if Ethyl's application for a waiver for MMT is granted. Our assessment mainly consisted of reviewing the toxicological and epidemiological literature on manganese. Our evaluation of health studies was based on factors such as the design of experiments, the quality of the data, sample size of studies, statistical methods used to analyze data, and conclusions drawn from statistical analyses. In some cases, attempts were made to replicate statistical calculations. As part of our assessment of the health literature, we considered the findings of EPA and the Health Effects Institute, two organizations that have conducted extensive reviews of the manganese literature. We also considered existing reviews of studies concerning health effects from manganese exposure.

To evaluate the body of toxicological and epidemiological data on health effects from manganese, we sought the advice of several recognized public health experts: Dr. Ian T.T. Higgins, Dr. Emanuel Landau, and Dr. Carl O. Schulz.[1] All of these individuals have participated in EPA reviews or have worked directly for the Agency. In addition, Dr. Higgins was the primary author of a key study on particulate matter for the

---

1.Curriculum vitae for these individuals and for Dr. Roth and Mr. Walker are Attachment A-1 to this report.

National Academy of Sciences, and Drs. Higgins, Schulz, and Landau, as well as Dr. Roth, have worked on an earlier Health Effects Institute document on manganese.

In addition to evaluating the health literature, we also qualitatively estimated the health benefits associated with using the Ethyl fuel additive. Ethyl has demonstrated that the use of their product would substantially reduce emissions of CO, NO_x, and aromatic hydrocarbons. Some of these substances have been shown to be closely associated with respiratory and cardiac conditions while others are known carcinogens. Thus, the benefits derived from reducing their emissions can be substantial.

In conclusion, we found that the use of MMT is unlikely to affect public health adversely. The anticipated increase of manganese in the environment from use of MMT is sufficiently small in comparison to the natural levels of this element and human intake of it that the body's ability to maintain consistent manganese levels should be unaffected. Indeed, small amounts of manganese are required by the body to maintain proper functioning. Thus, no adverse effect on health would be anticipated. Data concerning the impact of exposure to amounts of manganese such as those likely to result from the addition of MMT to gasoline are consistent with the lack of any adverse effect. Furthermore, use of MMT would lead to reductions in emissions of other compounds of health concern at or near ambient levels. Thus, the net effect of MMT use is likely to be a reduction in health risk.

Outline of Report: In addition to this introduction, our report is divided into six sections. An overview of the findings of EPA's evaluation of the health effects resulting from manganese exposures as well as an evaluation conducted by the Health Effects Institute is given in Section B. The EPA report assessed the health effects literature up until 1984 and the HEI report reviewed the literature up until 1988. The findings from the HEI report are of particular interest because it specifically

analyzed the impact of using manganese as a fuel additive. An evaluation of the epidemiological and toxicological literature since 1988 is given in Section C.

In Section D, we specifically address the issues raised by commenters in the EPA proceeding on MMT. According to emission test data generated by Ethyl, the MMT fuel additive will result in substantially reduced tailpipe emissions of NO_x, CO, benzene, and other toxics. A qualitative analysis of the benefits of the reductions is given in Section E. Section F contains a summary of our conclusions. Finally, Section G contains references.

B. HISTORICAL BACKGROUND

The question of whether manganese emissions might pose a threat to public health is not a new one. In 1984, EPA prepared a Health Assessment Document (HAD) "to summarize the current knowledge of the effects of exposure to environmental manganese upon human health."[1] More recently, the Health Effects Institute (HEI) examined potential health effects from increased public exposure to manganese as a result of the use of a possible manganese-containing fuel additive (not MMT).[2] Both of these assessments concluded that health effects were unlikely at the levels of manganese in the environment that would result from the use of MMT as proposed by Ethyl.

EPA's Health Assessment Document: EPA's HAD may be the most thorough existing discussion of human exposure to environmental manganese. It discusses environmental levels of the metal and human exposure through various media as well as human and animal studies of effects after toxic and chronic exposures. The present question, of course, involves chronic exposure.

Environmental Levels and Human Exposure

According to EPA, manganese is the twelfth most abundant element in the earth's crust and the fifth most abundant metal. HAD at 3-93. In 1982, the most recent year for which EPA included data, the annual arithmetic mean manganese concentration in urban air was 0.033 $\mu g/m^3$. Ambient air concentrations exceeding 10 $\mu g/m^3$ have been reported. HAD at 3-97. For purposes of comparison, Ethyl has indicated that use of MMT would lead to an expected maximum ambient air impact of 0.0009 $\mu g/m^3$.

1.U.S. Environmental Protection Agency, *Health Assessment Document for Manganese* (August 1984) (NTIS Document No. EPA 600/8-83-013F) at 1-1. This document appears in Attachment B-1.

2.Health Effects Institute, *Potential Health Effects of Manganese in Emissions From Trap-Equipped Diesel Vehicles: A Report from the Health Effects Institute* (September 1988). (Attachment B-2)

The average intake of manganese by an adult human is approximately 2.3 to 5.5 mg per day. Most of this intake (generally over 90%) is from food. HAD at 3-99. Under normal conditions, approximately 3 to 4% of ingested manganese is absorbed.

The body of a normal adult man contains approximately 12-20 mg of manganese. The highest concentrations occur in the liver and pancreas, with the brain and gonads having among the lowest concentrations. HAD at 4-6. Relatively stable levels of manganese in human tissues (including brain tissue) are maintained even with large variations in manganese intake. Only when truly heroic doses of manganese are administered (e.g. 10 mg/kg in rats) is there evidence that the mechanism for maintaining homeostasis may be overwhelmed. Regulation of manganese levels apparently involves both absorption and excretion. HAD at 4-13.

Neurotoxic Effects of Chronic Exposure

There is no question that inhalation of manganese at sufficiently high levels can produce neurological symptoms. The symptoms of such manganese neurotoxicity resemble those of Parkinson's disease and include tremor, jerkiness of movement, limb rigidity and postural disorders. HAD at 6-1. Most reported cases of such manganism have occurred in manganese miners. Others have occurred in workers in industries that produce dusts or fumes of manganese oxides. HAD at 6-12. Exposure levels in the studies of miners have been as high as 450 mg Mn/m^3 and in all of the reported studies reached at least 16 mg Mn/m^3. Levels of industrial exposure were somewhat lower, but in each study were at least 0.30 mg Mn/m^3. At these lower exposure levels, neurologic symptoms, rather than actual manganism, were reported. HAD, Table 6-4, pp. 6-13 - 6-14. Thus, the data provided no clear-cut evidence of chronic manganese poisoning under 5 mg Mn/m^3. HAD at 6-23.

If the 0.0009 $\mu g/m^3$ of manganese attributable to MMT is added to the 0.033 $\mu g/m^3$ present in ambient air, the resulting

concentration would be 0.034 $\mu g/m^3$. The lowest manganese level EPA found to be associated with manganism was 5 mg/m^3 (5,000 $\mu g/m^3$). Thus, the ambient concentration of manganese following MMT approval would still be over 5 orders of magnitude lower than the lowest level of manganese associated with manganism. Even a manganese contribution from MMT as high as 0.09 $\mu g/m^3$ would still leave ambient concentrations more than 4 orders of magnitude below those associated with manganism.

The lowest manganese exposure level at which EPA indicated neurological symptoms were reported (as opposed to manganism) was in the range of 0.3 to 20 mg/m^3 (300 to 20,000 $\mu g/m^3$). Saric, et al. (1977), reported neurological symptoms in 5.8% of plant workers exposed to this level of manganese. Those symptoms, however, could not be definitively attributed to the manganese exposure. HAD at 6-19. In any case, that exposure was still almost 4 orders of magnitude higher than the 0.034 $\mu g/m^3$ level that would be expected if manganese attributable to MMT were added to the ambient air, and over three orders of magnitude higher than ambient manganese levels if MMT results in a 0.09 $\mu g/m^3$ ambient manganese contribution.

Respiratory Effects of Chronic Exposure

The HAD also describes several studies supporting an association between pulmonary effects and exposure to manganese. However, as the HAD notes, "[m]ost of these exposures range higher than . . . 5 mg Mn/m^3, so they provide little information on the possible effects of exposures to ambient levels." HAD at 6-56. Nogawa, et al. (1973) is an exception, finding increased respiratory symptoms in children (a sensitive population, HAD at A-5) exposed to manganese dust from a ferromanganese plant at an ambient concentration that EPA estimated to be about 3-11 $\mu g/m^3$. HAD at 6-52.

Because the HAD concluded that respiratory effects are reliably reported at lower levels than any other effect[1], the HAD develops a lowest observed adverse effects level (LOAEL) and a no observed effects level (NOEL) for manganese based on the human and animal data concerning such effects. Based on the Nogawa study, the HAD indicates that the human LOAEL for manganese is 0.003-0.011 mg/m^3 (3-11 $\mu g/m^3$). HAD at 9-12. Based on a series of animal (rat and monkey) studies by Ulrich, et al. (1979a,b,c), the HAD indicates that the NOEL is 0.1 mg/m^3 (100 $\mu g/m^3$). HAD at 9-13. The estimated human equivalent intake to this NOEL is in the range of 51-87 $\mu g/m^3$. When a ten-fold margin of safety is added to protect sensitive individuals, this range becomes 5.1 to 8.7 $\mu g/m^3$. HAD at A-3. Thus, both the LOAEL and the NOEL estimated in the HAD are well above the level of ambient exposure that would be expected if MMT were added to gasoline in the amounts proposed by Ethyl.

Other Effects Following Chronic Exposure

Of the other types of effects alleged by commenters in the Ethyl waiver proceeding, the only one on which the HAD indicates the existence of some useful data is reproductive effects. According to the HAD, impaired sexual behavior has often been reported in workers showing symptoms of manganism. HAD at 6-68. While the HAD does not discuss the manganese exposure levels which have led to this impairment, exposures were apparently at the levels that have been associated with manganism, i.e., >5 mg/m^3. As discussed above, this manganese level is several orders of magnitude above the maximum level that would be expected in the ambient air if Ethyl's fuel additive waiver application is approved.

1.The Environmental Health Committee of EPA's Science Advisory Board questioned this conclusion because it felt that the Nogawa study "does not provide a sufficiently strong scientific basis to support the conclusions in the document. The pulmonary effects noted in these children might also be due to other compounds in the emissions." See Attachment B-3.

HEI Report: In 1984, in connection with its development of a manganese-containing fuel additive to be used with a particulate trap for diesel engines, Volkswagen asked HEI to examine health issues associated with manganese emissions resulting from the use of such a fuel additive. The resulting 1988 HEI Report revisits and updates the data concerning health effects from manganese exposure. In addition, it draws specific conclusions about the risk of health effects from manganese emissions leading to ambient manganese levels as high as 0.5 $\mu g/m^3$.

HEI concludes, "[I]t appears very unlikely that exposure to airborne manganese from mobile sources (worst-case level 0.5 $\mu g/m^3$) would produce adverse neurologic effects," and, "[I]t appears unlikely that the increased ambient levels of manganese from trap-equipped diesel vehicles would produce adverse respiratory effects." HEI Report at 2-3. HEI bases these conclusions on an evaluation of the health effects data and on a comparison of manganese from automobile exhaust to dietary intake of manganese. HEI report at 34-36.

Moreover, having identified iron-deficient individuals and the very young as potential high-risk groups, HEI concludes that these individuals are unlikely to be harmed as a result of manganese added to the air as a result of manganese-containing fuel additives. HEI states, "While the susceptibility of these groups may be observed in . . . studies [in which dietary manganese is increased by a factor of 7 or more above normal, or manganese is intubated daily at even higher levels] the actual dose inhaled from automobile-derived, airborne manganese will remain exceedingly small compared to the normal dietary range." HEI Report at 34.

While HEI identifies some studies that post-date the HAD (e.g., Roels, et al. [1987a,b]), the studies that HEI identifies as suggesting possible neurological and respiratory effects at the lowest levels are the same studies identified in the HAD -- Saric, et. al. (1977) and Nogawa, et al. (1973). HEI undertakes a brief critical evaluation of each of these studies that leads it to question the validity of the conclusions of each study.

Neurological Effects

Consistent with the HAD, the HEI Report indicates that Saric et al. (1977) reported neurologic effects (most commonly tremor at rest) in industrial workers exposed to manganese levels as low as 0.3 mg/m^3. This was the lowest level at which neurological effects had been reported.

The HEI Report, however, indicates several shortcomings of the Saric study. First, tremor could not be attributed solely to manganese. Possible confounding factors such as the presence of other metals, carbon monoxide, carbon dioxide and coal dust and the existence of alcoholism were not considered. Documentation of important factors -- the methods used in neurological examinations, occupational histories of subjects and exposure duration -- was inadequate. Moreover, the inconsistency of finding a correlation of subjective symptoms, but not neurological ones, with smoking was not resolved. HEI Report at 19-20.

Thus, while the HEI Report indicates that neurotoxic effects are well documented in individuals exposed to manganese concentrations of 1 mg/m^3 or higher, effects at lower levels such as those in the Saric study are less certain. Even accepting the Saric study at face value, the 0.5 $\mu g/m^3$ manganese concentration expected from the diesel fuel additive was judged to be very low as compared to the lowest level in the Saric study. The ambient level of manganese resulting from Ethyl's proposed use of MMT would be lower still.

Respiratory Effects

While recognizing that Nogawa et al. (1973) reported respiratory symptoms in children at low levels of manganese exposure (although the levels were still two to three orders of magnitude above that anticipated by Ethyl as a result of the proposed use of MMT), HEI concluded that the Nogawa study was not reliable. HEI Report at 36. HEI noted that the difference in the prevalence of subjective symptoms was "relatively modest," only slightly above what would be expected on the basis of chance alone. In addition, the individuals performing the pulmonary

function testing were not blinded with respect to the exposure group to which individual subjects belonged. Moreover, there is no indication that the pulmonary function measurements were adjusted for height, weight, age and sex. Confounding factors such as parental smoking and socioeconomic status do not appear to have been considered. Finally, exposure levels were not well defined. HEI Report at 22-23.

Since all other studies that suggest adverse respiratory effects from manganese exposure involved levels one or two orders of magnitude greater than that in Nogawa, HEI concludes that the 0.5 $\mu g/m^3$ exposure to manganese expected from the diesel fuel additive is much lower than "the levels at which adverse health effects have been observed in reliable epidemiologic studies." HEI Report at 36.

HEI goes on to state, "If the objections to the Nogawa study are ignored, and its results are taken prima facie, the difference between the lowest observed adverse effect level in the Nogawa study (3 μg Mn/m^3), and the worst-case manganese level from trap-equipped vehicles (0.5 $\mu g/m^3$) is not very large. The estimated worst-case manganese level is also only 10-fold lower than the no observed effects level calculated from animal studies." HEI Report at 36.

It should be noted, however, that even if the results of the Nogawa study are accepted, there is a 100-fold margin of safety between the lowest level of manganese exposure associated with effects in that study and the manganese exposure that is predicted to result from exposure to MMT. Instead of the 0.5 $\mu g/m^3$ manganese concentrations expected to result from the diesel fuel additive considered in the HEI Report, the proposed use of MMT is projected to create a maximum ambient concentration of 0.034 $\mu g/m^3$. Thus, the margin of safety is an order of magnitude larger than that for the diesel additive.

We were also asked, however, to consider the possible health impact if the contribution to ambient manganese levels due to MMT were 0.09 $\mu g/m^3$. In that case, total ambient manganese would be approximately 0.12 $\mu g/m^3$. This is still less than a quarter of the level (0.5 μ/m^3) considered safe in the HEI Report.

Moreover, it is almost 30 times lower than the lowest level in the Nogawa study. Based on our evaluation of the Nogawa study (summarized below), we are comfortable that this margin of safety assures protection of public health.

Summary and Conclusions: There is no question that elevated levels of manganese are associated with pulmonary and neurotoxic effects, but these effects apparently occur only at levels that are at least three orders of magnitude higher than ambient levels that would result from emissions of the Ethyl fuel additive. In addition, manganese is an essential element for human health. Given all of this, there is no reason to expect that ambient manganese levels resulting from the Ethyl fuel additive will cause harmful effects to man.

C. NEW HEALTH STUDIES

In the previous section, we summarized findings from the 1984 EPA Health Assessment Document and the 1988 HEI Report on manganese. These two documents provide a comprehensive review of the epidemiological and toxicological literature on manganese prior to 1988. Since that time a number of relevant studies have been published. In this section we will briefly summarize the findings from key health studies of manganese published since the 1988 HEI Report and assess them. More detailed reviews of several of the studies are given in the appendices accompanying this section.

Specific Studies: As stated above, the principal health effects that have been associated with manganese exposures are neurotoxic effects and respiratory symptoms. The most credible study which found effects at the lowest levels of manganese (at about the 300 $\mu g/m^3$ level) is Saric et al. (1977), which was reviewed in the 1988 HEI report. In brief, the HEI report found that even Saric et al.'s findings were unconvincing because some of the results were counterintuitive with a manganese association. For example, individuals exposed to lower levels of manganese appeared to suffer a higher incidence of central nervous system effects than individuals who were exposed to higher levels. Also, the study suffered from several design flaws.

The only study which examined respiratory systems at near ambient levels of manganese is Nogawa et al., another study that was examined in the HEI report. Below, we include a review of this study.

In addition, we review the following studies that have been completed since the HEI report was issued. Gottschalk et al. (undated) examined manganese levels in the hair of individuals jailed on charges of committing violent crimes. Stauber and Florence (1989), Hams and Fabri (1988), and Cawte et al. (1989) were studies which examined residents of Groote Eylandt, who are typically exposed to high levels of manganese. Roels et al.

(1987), Wang et al. (1989), Huang et al. (1989), and Phoon (1988) examined industrial exposure to manganese. Nogawa et al. (1973) looked at the lung and pulmonary function of teenagers living in an area of high manganese concentration. Bleecker (1988) examined the neuro-toxicological differences between Parkinson's disease and manganese-induced parkinsonism. Donaldson (1987), Abbott (1987), and Cooper (1984) are review articles which examined the effects of manganese.

Gottschalk et al. (undated)
Stauber and Florence (1989)

Gottschalk et al. reported that manganese levels in the hair of violent prisoners were significantly elevated as compared to control groups. Three different pairs of cohorts were considered in his study, which he informed us has now been rejected for publication in Neurotoxicology. First, 104 inmates at the Deuel Vocational Institute in Stanislaus, California were compared to a control group of 52 individuals in the town and a control group of 31 guards at the prison. Second, 60 prisoners at the Los Angeles Bernardino facility were compared to 42 town controls. Finally, 24 inmates at the San Bernardino County Jail were compared to 59 town controls. In every comparison, controls were supposed to be matched to inmates by age, sex, and race. The levels of airborne and dietary manganese to which subjects were exposed were not measured.

The authors found that, in general, manganese levels were higher among inmates than in controls. They claim this suggests that "A cofactor such as alcohol, dietary deficiencies, or psychosocial factors, might act in combination with mild manganese toxicity to precipitate violent behavior." This conclusion does not consider the source or cause of the elevated manganese. For example, a single unknown condition could lead to high levels of manganese in hair and violent tendencies in an individual. Thus, the manganese would not be a cause of the violence.

For several reasons, it is difficult to accept the findings from Gottschalk et al. of higher hair manganese levels in violent prisoners. First, it is obvious that controls were not carefully

matched to inmates by race. For example, in the first study, 39 Caucasian, 33 Hispanic, and 32 Black prisoners were matched to 62 Caucasians, 10 Hispanics, and 11 Blacks. This is very important because race and hair color (a factor related to race) are associated with differences in hair manganese levels. (Sky-Peck [1990], Attachment C-1). Since blond hair occurs more frequently in Caucasians who predominate among the controls, this could explain the observed differences.

Second, no information is given on how subjects were matched for age, and there is reason to doubt the method used to match age. As Dr. Landau pointed out (Attachment C-2): "Mean age is used instead of the more useful median used in demographic research. This reviewer is unable to find acceptable a process of age matching which could result in a mean age of 29 years for the violent prisoners versus a mean age of 24 years for the town controls and a mean age of 31 years for the guards."

Third, the study fails to account for factors other than toxic metals that might affect violent behavior. Factors such as alcohol or drug usage, smoking, social factors, medical and occupational histories, and recent traumas are ignored. The social science literature is replete with data that discuss the significance of these factors in explaining violent behavior. It is therefore surprising that none of these factors was considered in the study.

Fourth, the study findings are suspect because of the apparent instability of the manganese levels in the hair of prisoners. In the first cohort, the mean level of manganese in hair was 2.0 ppm; in the second cohort it was 1.39 ppm; and in the third cohort it was 0.71 ppm. In fact, the Deuel guards had comparable levels of manganese to the San Bernardino violent prisoners. As Dr. Higgins observes (Attachment C-3): "It may be significant that the manganese concentrations in the prisoners in the three phases has been declining. Just one more phase might show no significant difference."

Finally, an extremely serious shortcoming of this study is that it has been shown by Stauber and Florence (1989) (Attachment C-4), who studied a population with some of the highest manganese

exposures in the world (the Groote Eylandt Aborigines), that manganese concentration in hair in a high manganese environment is not a good indicator of manganese body concentrations, because high scalp hair manganese values are "due largely to manganese from exogenous sources." Stauber and Florence also found, "Measurements of manganese in hair and blood of Groote Eylandt Aborigines showed that the population had a high exposure to manganese, but did not distinguish between those individuals affected/unaffected by the neurological condition, Groote Eylandt Syndrome." Given that Stauber and Florence failed to find a relationship between hair manganese levels and neurological effects among the Groote Eylandt Aborigines (i.e. a highly exposed population), it is difficult to accept the conclusion of Gottschalk et al. of effects from manganese levels experienced by the general American population.

Hams and Fabri (1988)

Hams and Fabri (Attachment C-5) measured blood manganese levels for 40 Australian aborigines living near a surface manganese ore deposit on Groote Eylandt, Northern Territory. These were compared to levels measured among a control group of 15 unexposed laboratory workers. The mean manganese level among the exposed group was found to be 490 nmol/L compared to 215 nmol/L for the control group.

Hams and Fabri noted an apparent "association between very high concentrations of manganese in blood, low serum iron, and the occurrence of a group of neurological disorders that have a prevalence of about 2%." They explained that "The group of aborigines showing symptoms of neurotoxicity ... may have unusual or defective manganese regulatory processes."

These results, together with the results of Cawte et al. (1988) suggest that neurologic disorders seen among certain aborigines living on Groote Eylandt are the result of a complex combination of factors not present in the U.S. Moreover, while no specific manganese exposure levels are given, the levels are almost certainly far higher than those in the United States.

Thus, use of these people for ascertaining an exposure-response relationship for U.S. population exposed to airborne manganese is inappropriate.

Cawte et al. (1989)

Several commenters to the docket (Donaldson, Hodges, and Silbergeld) have cited the incidence of a motor neuron disorder resembling Parkinson's disease among native people living on Groote Eylandt in the Gulf of Carpentaria, Northern Australia as an example of manganese toxicity suggesting that these individuals display greater sensitivity to the toxic effects of manganese than other occupationally-exposed populations that have been studied. The residents of Groote Eylandt have also been cited as exemplifying the ability of manganese to induce violent personality disorders (Hodges, Gottschalk et al). Cawte et al. (1989) (Attachment C-6) examined the information available on this motor neuron disease and hypothesized that this syndrome is not simple manganism but rather manganism influenced by several factors.

The authors pointed out that the symptomology in Groote Eylandt is different from that described for Chilean manganese miners and is more like that described for manganese-exposed individuals in Egypt. The important potential synergistic factors identified by the authors include genetic factors such as inborn errors of trace element metabolism (there is a high prevalence of Wilson's disease among Groote Eylandters; neurological symptoms occur predominantly in two clans); lifestyle characteristics (these people cook in the earth and seldom wash); dietary deficiencies of dopamine oxidation inhibitors, calcium, and iron (potentially resulting in enhanced manganese absorption); and smoking and excessive alcohol intake. These factors, plus the uniquely high level of ambient manganese to which they are exposed, make the aborigines of Groote Eylandt inappropriate models for the population of the United States in assessing the potential health effects of exposure to low levels of manganese in the environment.

Roels et al. (1987)

A group of 141 workers exposed to inorganic manganese in a manganese oxide and salt producing plant was compared with a matched group of 104 subjects. The time-weighted average concentration of total airborne dust during the survey ranged from 0.07 to 8.61 mg/m^3 Mn. Except for rigidity of trunk, standardized neurological examinations did not reveal any specific differences between control and manganese-exposed workers. Psychomotor tests, short-term memory tests, and hand tremor evaluations revealed deficits in the manganese-exposed group.

Manganese exposures in the Roels study are substantially higher than the ambient levels that would result from the use of the Ethyl fuel additive. The lowest level in the Roels study was 70 $\mu g/m^3$ as compared to the .034 $\mu g/m^3$ that would result from the Ethyl fuel additive.

In addition, it is questionable whether Roels' findings are valid because no monitoring data were available to characterize past manganese levels, there appear to be problems in the way smoking data were analyzed, and the study had some design flaws. For a more thorough discussion of these problems, see Attachment C-7.

Wang et al. (1989)
Huang et al. (1989)

Wang et al. (1989) (Attachment C-8) and Huang et al. (1989) (Attachment C-9) both report on the same outbreak of manganese-induced parkinsonism. Workers were exposed to manganese concentrations as high as 28.8 mg/m^3 in a ferromanganese smelter. The high concentrations of manganese were most likely caused by a defective ventilation system. It is not clear how long the workers were exposed to elevated manganese levels, although Huang et al. (1989) report that "all patients worked for more than 2 years in the direct vicinity of the furnace without any protective equipment." Wang et al. (1989) report that workers were exposed "for 30 minutes each day, seven days a week, to high concentrations of air manganese (>28.8 mg/m^3)."

Six of eight workers exposed were diagnosed by standard neurological examination to have developed "parkinsonism". All of the men had been employed for 10 years or more. Furnacemen who were exposed to 0.5-1.5 mg/m^3 manganese at the same factory showed no such symptoms. Patients who developed "parkinsonism" were treated with levodopa and carbidopa daily for 8 weeks, which appeared to improve the neurological symptoms by 50%. After fixing the ventilation system, the air concentration of manganese was reduced to below 4.4 mg/m^3, and no new cases of "parkinsonism" have been observed.

The relevance of these findings to our present investigation is uncertain due to the extremely high manganese levels present in this case. Also, it is not clear whether race plays an important factor in this case. The absence of neurological symptoms among workers at the plant who were exposed to less extreme levels of manganese (although still several orders of magnitude higher than levels expected to follow use of MMT as a fuel additive) provides assurance that the levels of manganese due to MMT will not be detrimental to human health.

Phoon (1988)

In a brief review article, using only primary source material, Phoon (1988) (Attachment C-10) examined whether there might be some biological index of exposure to manganese (BEI) that is correlated with the risk of intoxication by this metal. Phoon hypothesized that blood or, preferably, urine levels of manganese might be used to monitor manganese exposure for workers exposed to high concentrations. He concluded that the available data were not adequate to support the establishment of such a BEI. Phoon's review indicated that there was no direct relationship between blood or urine manganese levels and the occurrence or severity of poisoning. Some individuals with symptoms of manganese intoxication have blood levels within the normal range, suggesting that individual susceptibility plays a role in the development of these signs and symptoms.

Nogawa et al. (1973)

Although this paper was reviewed in the 1988 HEI report, it is important to review the findings of this study again because HEI suggested it warranted further analysis if approval of a manganese fuel additive was sought. There is much convincing data in the literature that shows an association between high levels of manganese (1 mg/m^3 or higher) and bronchitis among workers, but at levels below .4 mg/m^3 there appears to be no risk. Nogawa et al. (1973) (Attachment C-11) suggests, however, that among children these effects might be associated with manganese levels in a range estimated to be 3-11 $\mu g/m^3$.

In brief, Nogawa et al. (1973) found that the pulmonary performance of children living near a ferromanganese plant was slightly worse than the performance of children living at a distance from the plant in a city. Both physiological tests as well as subjective tests based on the British Medical Questionnaire were administered in the study. No direct ambient measurements of manganese were taken; thus, true manganese exposure levels are unknown. By using data from West Virginia, however, EPA estimated that levels in Nogawa et al. ranged from 3-11 $\mu g/m^3$.

HEI, as well as Drs. Landau and Higgins (Attachments C-12 and C-13), all concluded that the study suffered from major flaws which could have invalidated the study findings. Some of these flaws were: the study might have been biased because it appears that neither students nor testers were blinded; it is questionable whether the data were adjusted for age, sex, height, and weight; the study did not appear to consider social factors; serious doubts remain as to the exposure levels in the study; and exposure to pollutants other than manganese was not considered.

Bleecker (1988)

Bleecker (1988) (Attachment C-14) reviewed the state of knowledge regarding the induction of the symptom complex of parkinsonism by four neurotoxic agents including manganese in order to determine whether these agents have a common site of action. Based on differences in neuropathology and clinical

symptoms, the author distinguishes between parkinsonism and Parkinson's disease. She points out that the symptoms of manganese-induced parkinsonism, which strongly resembles Parkinson's disease, include fixed gaze, bradykinesia, postural difficulties, rigidity, tremor and dystonia, and prominent mental status changes. The latter two symptoms distinguish manganese intoxication from Parkinson's disease.

At the neuropathological level the differences between manganese intoxication and Parkinson's disease are even more striking. Manganese affects primarily the striatum palladium, an area of the brain that is not affected by Parkinson's disease. Lewy bodies, a marker of Parkinson's disease, have never been observed in manganese intoxication.

Bleecker concludes that the neuropathologic features of Parkinson's disease and manganese-induced parkinsonism differ diametrically with Parkinson's disease affecting primarily the substantia nigra and manganese affecting the striatum and globus pallidus. This conclusion is inconsistent with the hypothetical construct of Donaldson (1988) that Parkinson's disease may be the result of cumulative manganese intoxication in the elderly.

Donaldson (1987)

Donaldson (1987) (Attachment C-15) is a review article by one of the commenters in this proceeding. The subject of the review is neurological effects of manganese exposure. Thus, the symptoms of manganism are discussed. The affinity of manganese for the melanin-containing substantia nigra region of the brain is indicated. The article indicates that neuromelanin in this region is formed from nonenzymatic oxidation of dopamine.

The author discusses possible explanations for manganese neurotoxicity. It is hypothesized that the mechanism for manganese neurotoxicity is the destruction of dopamine and other catechols by Mn^{3+}. It is further hypothesized that the neurological symptoms seen in some residents of Groote Eylandt are the result of excessive amounts of manganese and deficiencies in calcium.

The article is of little value in assessing the potential impact of MMT use on human health. The fact that high levels of manganese can lead to neurological symptoms is well-established. This article does not discuss the levels of manganese involved in the examples of neurotoxicity it cites. Moreover, the hypotheses about mechanisms for manganese toxicity are not supported by any data. Thus, the article adds nothing more than speculation to the information considered in the HEI report.

Abbott (1987)

Abbott (1987) (Attachment C-16) is essentially a review article. It deals directly with the potential impact on health of MMT use in gasoline. Estimating that the expected increase of manganese in ambient air as a result of MMT use would be approximately 0.2 $\mu g/m^3$ in areas of high traffic density and adding that to the current ambient level of 0.01 $\mu g/m^3$ in urban areas in Australia, Abbott concludes that no health risk from the use of MMT is likely.

Abbott reaches this conclusion after reviewing the data on the effect of manganese on human health. He concludes that potential toxicological effects of increased airborne manganese are restricted to the pulmonary and central nervous systems. The possibilities of oncogenicity and reproductive effects are considered and dismissed. Since animal and human data to date suggest that long-term exposure to "relatively high levels" of manganese are needed to produce symptoms of toxicity, the increased level of airborne manganese from the combustion of MMT is not likely to constitute a health risk to the general population.

Abbott estimates ambient manganese levels following the use of MMT from data on the ratio of lead levels in gasoline and air. Thus, his estimates of the effect of MMT on ambient manganese levels are uncertain. He bases his conclusions about health risk, however, on ambient air levels higher than those that Ethyl has indicated would result from its proposed use of MMT even if half the manganese added to gasoline were emitted from the tailpipe following combustion. Thus, his conclusions can be applied to evaluate the Ethyl proposal. His conclusions are

consistent with ours that approval of Ethyl's waiver application would not be anticipated to cause any adverse effect on health.

Cooper (1984)

Cooper (1984) (Attachment C-17) is another review of the health consequences of adding MMT to gasoline. Cooper's conclusions are consistent with those in our report.

Specifically, "There appears to be an extremely wide margin of safety between the airborne concentration of manganese that has been associated with central nervous system disease in humans and experimental animals and those that might be found in ambient air resulting from the use of MMT." Cooper at 37. "Although manganese is probably more readily absorbed in infants and crosses the blood-brain barrier more readily, all available evidence would indicate that the amounts of manganese added to ambient air by MMT would fall within the range of normal daily absorption and would not cause neurologic effects, even in the most susceptible portion of the population." Cooper at 37. "[I]t appears extremely unlikely that minute increments in airborne manganese even as great as 1 or 2 $\mu g/m^3$ would have any detectable effect on the lungs." Review of other possible effects on the cardiovascular, hematopoietic and reproductive systems and of the possibility of mutagenesis or carcinogenesis also did not suggest that MMT combustion would have any effect on health.

Summary: The HEI report found no health threat to the general population from the airborne levels of manganese which would result from the use of the Ethyl additive. Our review of more recent literature supports that conclusion. Furthermore, our evaluation of the Nogawa et al. (1973) study confirms the conclusion of the Environmental Health Committee of EPA's Science Advisory Board and HEI that the study is seriously flawed and cannot be relied upon to support concern about respiratory effects from airborne manganese at concentrations below 300 $\mu g/m^3$.

D. ISSUES RAISED IN THE EPA DOCKET

This section addresses the specific concerns raised by five commenters on Ethyl's application for a waiver. Health concerns were set forth by the National Institute of Environmental Health Sciences (NIEHS), the Environmental Defense Fund (EDF), Mr. Everett L. Hodges, Dr. John Donaldson, and Dr. Herbert L. Needleman.

National Institute of Environmental Health Sciences: There are essentially eight points of concern which were laid out by the Director of NIEHS. These concerns are addressed in detail by Dr. Carl Schulz in Attachment D-1. We respond briefly to each of these concerns in the following paragraphs.

(1) Manganese is toxicologically similar to lead.

This issue is examined in depth by Dr. Schulz in his essay "Contrasting Public Health Concerns Raised by Lead, Manganese, and MMT" (Attachment D-2). In summary, there are profound chemical, biological, and environmental differences between lead and manganese.

Chemically, while lead is a "heavy" metal, manganese is a "light" one. Thus, the chemical reactions of manganese resemble those of chromium and iron rather than those of lead.

The biological differences between lead and manganese are particularly striking. The body's need for and ability to regulate levels of manganese are well-established. Manganese is an essential trace element in human and animal nutrition, while lead has no known biological benefit. Homeostatic mechanisms regulate the uptake and excretion of manganese in higher animals and man. There is no known similar mechanism for lead. Moreover, while much of the lead to which humans are exposed is retained in the bone and has a half-life of over twenty years, manganese is eliminated with a half-life of approximately 38 days.

Environmentally, manganese is far more common than lead. Humans are exposed to relatively high concentrations of manganese through food, water, and air. In the absence of anthropogenic sources, human exposure to lead is one to two orders of magnitude less than to manganese.

(2) MMT is readily absorbed via the nose, resulting in higher levels of manganese in the central nervous system than result from comparable doses by other routes.

MMT is not emitted in measurable amounts from the tailpipe of cars fueled by gasoline to which MMT has been added. The emissions are in the form of manganese oxides. Inhaled manganese oxides are eliminated by normal clearance mechanisms or may be absorbed into the general circulation. In the latter case, their dissolution products must pass through the heart, lungs, and probably the kidneys and liver, before reaching the brain. There is no shortcut from the nose to the brain as seems to be implied by this concern.

(3) The effects of manganese on the central nervous system are not reversible "easily, if at all."

The World Health Organization (WHO) concluded that the neurological damage attributable to high-level manganese exposure is at least partly reversible if the patient is removed from exposure at an early stage. The symptoms of manganism can be treated by administration of L-Dopa (WHO 1981). Effects on the central nervous system are, in any case, not anticipated from the manganese levels expected to result from the addition of MMT to gasoline.

(4) Information about the "fate" of burned manganese is not adequate to explain the small quantity measured in exhaust.

We have not addressed this concern directly, since it is not a health issue. However, even if forty percent of the manganese added were released in the exhaust (100 times the amount that Ethyl measured in tailpipe emissions tests), the levels of manganese in ambient air would be below levels where health effects are seen.

(5) Humans may be exposed to Mn_3O_4 or other oxides/salts which are more toxic than MnO_2.

While no documentation for these assertions is given, they are probably based on the relative oral toxicity of these compounds in laboratory animals. Since most animals lack the substantia nigra region that is apparently the target of manganese in humans (Donaldson, 1987), the relevance of data on comparative toxicity in animals to the potential human health hazards resulting from chronic exposure to low concentrations of these two forms of manganese in air is unclear. Moreover, all forms of manganese are apparently metabolized to Mn^{3+} in the brain. (Donaldson, 1987). Therefore, the original form of the manganese would appear unimportant, at least with regard to the neurotoxic effects of concern to NIEHS.

(6) MMT is as toxic as tetraethyl lead.

Since it is not one of the combustion products, MMT is not the issue with regard to the combustion of MMT-containing gasoline in automobiles. As discussed above and in Attachment D-2, manganese oxides, which are emitted, are not comparable chemically, biologically, or environmentally to compounds of lead.

(7) The epidemiologic studies of manganese are based on high concentrations which may be irrelevant for the low-dose exposures to the manganese forms which will result from use in gasoline.

Epidemiologic studies are incapable of detecting low incidences of subtle health effects because of the lack of statistical power. Thus, such studies are commonly conducted in relatively small cohorts of highly exposed individuals to maximize the probability of a significant outcome. It is asking too much of epidemiologic methods to rely on such studies to provide quantitative dose-response data within the range of expected environmental exposures. Toxicological studies are better suited to identifying subtle effects from low-dose exposures. The conclusions in this report are therefore based on toxicological studies as well as epidemiological studies.

(8) Manganese may act via the same mechanisms as other heavy metals (especially lead), and may have synergistic effects.

This assertion once again raises the issue of parallels between manganese and lead. As previously indicated, there are profound chemical, biological, and environmental differences. The suggestion of synergism is unsupported generalized speculation.

Dr. Herbert L. Needleman: Dr. Needleman's comments raise two points. First, he draws an analogy between MMT and lead. MMT emissions are not expected from automobiles using gasoline to which MMT has been added. Therefore the concern is irrelevant.

Second, Dr. Needleman states that manganese is a neurotoxin. He indicates that it affects motor control and is related to Parkinson's disease. At sufficiently high concentrations (>5 mg/m^3), inhalation of manganese does cause a syndrome clinically similar, but not identical, to Parkinson's disease. The maximum level of manganese in air anticipated to result from the proposed use of MMT in gasoline, however, is several orders of magnitude below the level associated with this syndrome. Moreover, it is several orders of magnitude below the level at which even minor neurological symptoms have been reported. Thus, MMT added to gasoline is not anticipated to lead to neurological effects.

Everett L. Hodges: Mr. Everett L. Hodges opposes approval of MMT use because of a concern that elevated levels of manganese in the hair is associated with violent, criminal behavior. This concern is based on an unpublished study by Gottschalk, et al., of manganese levels in the hair of California prisoners, and the suggestion that Australian aborigines from Groote Eylandt have elevated levels of manganese in their hair. This part of the Australian continent has the highest incidence of murder and violence.

As discussed above, Dr. Gottschalk's paper is seriously flawed. Thus, it is not surprising that Neurotoxicology has declined to publish it. Certainly, the study is not of the quality to provide meaningful support to a theory as novel as that advanced by Mr. Hodges. Indeed, Dr. Gottschalk's study, even if valid, does not indicate that increased levels of airborne manganese would lead to increased violence. Dr. Gottschalk's paper, at most, indicates an association between manganese and violence. It does not indicate a causal relationship. Nor does it suggest that the excess manganese in hair is due to elevated airborne manganese levels.

In addition, the Groote Eylandt example does not support Mr. Hodges' concern. First, the allegation of violence among Groote Eylandt residents is not supported. Furthermore, while Groote Eylandters are exposed to manganese at levels sufficiently high to trigger neurological symptoms, Stauber and Florence (1989) report that there is no relationship between these symptoms and the levels of manganese in their hair.

Dr. John Donaldson: Dr. Donaldson, in comments presented in the hearing, supported Mr. Hodges' concern about a possible link between manganese and criminal behavior. As discussed above, that concern is without basis.

Dr. Donaldson, orally and in a 1988 report drafted for the Canadian government, hypothesized that early exposure to low levels of manganese may contribute to premature senescence. The purported mechanism for this effect is accelerated attrition of neuronal population in the substantia nigra. As a person ages, normal neuronal attrition increases which, he alleges, is added to the earlier effect of manganese. This leads to initial manifestations of Parkinson's disease when 75-80% of the neurons of the zona compacta of the substantia nigra have been lost. Linkage to other neurological disorders such as Alzheimer's disease and amyotropic lateral sclerosis (ALS) is also hypothesized. Dr. Donaldson admits, however, that the mechanism by which manganese produces nervous tissue and behavioral

toxicity is not known and that the concept of sub-clinical neuronal damages potentiating a chronic neurologic disorder has not been tested. Donaldson (1988) at 92-93.

As Dr. Donaldson essentially admits, this concern is nothing more than an untested hypothesis. See also Attachment D-3. It is one possible interpretation of the available data on effects of manganese, but it is based upon significant leaps of faith. For example, there is no evidence that low levels of manganese injure the neurons of the substantia nigra. Nor has it been demonstrated that Parkinson's disease, ALS, and Alzheimer's disease are caused by similar mechanisms. In fact, the evidence indicates that the mechanisms and neuropathy of manganism are distinguishable from those of Parkinson's disease. Mena et al. (1967); Barbeau (1984); Bleecker (1988).

The other concerns about possible health effects from exposure to very low levels of manganese that Dr. Donaldson expresses in his Canadian paper are likewise unsupported by scientific evidence.

Environmental Defense Fund: Dr. Ellen Silbergeld, on behalf of the Environmental Defense Fund, argues that manganese, like lead, is a neurotoxin. As discussed previously, manganese and lead differ significantly from chemical, biological and environmental perspectives. Moreover, while manganese is a neurotoxin at very high levels, there is no suggestion of neurological effects attributable to exposures to less than 300 $\mu g/m^3$ of manganese. Ambient exposures even with the use of MMT in gasoline are not expected to exceed 0.034 $\mu g/m^3$ and would be approximately 0.12 $\mu g/m^3$ even if it is conservatively assumed that 40 percent of the manganese added as MMT were emitted from the tailpipes of cars. Thus, there is a margin of safety from neurological effects of at least 3 orders of magnitude and probably 4 orders of magnitude.

Dr. Silbergeld also indicates that manganese is a lung toxin. While there is evidence of respiratory effects from exposure to very high levels of manganese in mining and several industrial operations, there is no reason to expect such effects

from the manganese added to the air through the use of MMT. The lowest observed adverse effects level and the no observed effects level developed by EPA for respiratory effects from manganese are both well above the highest level of manganese level anticipated in the ambient air if Ethyl's application for a waiver for MMT is granted.

In addition, Dr. Silbergeld states that manganese may affect the aging brain since it damages the nigrostriatal system. As Dr. Carl Schulz indicates in Attachment D-4, this claim is based on speculation advanced by Dr. John Donaldson. It assumes that manganese neurotoxicity and other neurological diseases associated with aging (e.g. Parkinson's disease and amyotropic lateral sclerosis) operate through similar mechanisms. The mechanism and neuropathy of manganism, however, are demonstrably different from those of Parkinson's disease. (Barbeau, 1984; Bleecker, 1988). There is no evidence that manganism operates by the same mechanism as other neurological diseases.

Dr. Silbergeld also expresses concern about possible fetal and reproductive effects from the manganese released as a result of MMT combustion. The only evidence for such effects, however, is at levels far above those that would result from the use of MMT. Possible reproductive effects were discussed by EPA in the HAD, but were not the basis for EPA's LOAEL or NOEL because there was evidence of such effects only at levels of at least 5 mg/m^3. Possible effects in the very young were considered in the HAD, but were associated only with massive doses of manganese salts orally or by intubation. Thus, they were not considered a concern even at levels an order of magnitude above those likely to result from MMT use.

Finally, Dr. Silbergeld alleges that manganese is a "cumulative toxin" and that data are lacking on long-term exposure to low levels of manganese. In fact, humans are constantly exposed to far higher concentrations of manganese in food and water than in air. Manganese is an essential element. As noted in the HAD, a document for which Dr. Silbergeld served as a peer reviewer, "manganese metabolism is rigorously controlled by homeostatic mechanisms. . . . The absorption, retention, and excretion of manganese are interrelated and

respond very efficiently to an increase in manganese concentration." HAD at 4-21.

Summary: In summary, none of the three major issues raised by commenters on the Ethyl application is of concern. First, manganese is very different from lead chemically, biologically, and environmentally. Thus, the experience with lead as a gasoline additive cannot be used as a model of what will happen if MMT is added to gasoline. Second, while high levels of manganese (i.e. >300 $\mu g/m^3$) are associated with neurological effects, concern that exposure to the far lower manganese levels expected to result from MMT use (e.g. 0.034 to 0.12 $\mu g/m^3$) has no basis. Finally, the concern that manganese causes violent criminal behavior is essentially speculation. The one study that indirectly supports it is seriously flawed. Similarly, none of the other concerns raised by commenters provide a basis for concluding that the addition of MMT to gasoline as proposed by Ethyl would endanger public health.

E. QUALITATIVE ANALYSIS OF BENEFITS FROM POLLUTANT REDUCTION

It is clear that use of MMT as a fuel additive will lead to some increase in levels of airborne manganese. The health significance of these increases has been the focus of previous sections. The addition of MMT to gasoline, however, will lead to significant reductions in emissions of several airborne pollutants. In this section we will examine the impact of MMT use on emissions of other pollutants and provide an analysis of the benefits from their reduction.

Data on emissions reductions are given in Attachment 7 of Ethyl's waiver application. Estimates are given for the year 1999, since the additive has a "long-term emission reduction effect." The largest reductions would be in nitrogen oxides and carbon monoxide although there are important reductions in other pollutants. In addition to reduced tailpipe emissions, there would be reduced emissions from refineries.

Nitrogen Oxides (NO_x): Use of MMT as a fuel additive would lead to a reduction in NO_x emissions of approximately 0.18 gm/mile traveled. This represents a 20% reduction in NO_x emissions from current levels for automobiles. Since automobile emissions make up approximately 45% of the total NO_x emissions in the environment, this is a sizable reduction in total NO_x.

For all the U.S. combined, this decrease in NO_x, amounts to 633 million pounds per year. When considering the additional reductions of NO_x emissions from refineries, the total reduction in NO_x emissions would be 644 million pounds per year.

NO_x is a criteria pollutant based, in part, on the potential for health effects from exposure to elevated NO_x levels. Most of the country, with the exception of Los Angeles, California, however, attains the primary national ambient air quality standard for NO_2 (the regulated form of NO_x). [U.S. Environmental Protection Agency, National Air Quality and Emissions Trends Report, 1987, (March 1989) (NTIS Document No.

EPA 450/4-89-001) at 12. (Air Quality Trends.)] Since this standard protects the public health with an adequate margin of safety, 42 U.S.C. §7409(b)(1), further reductions in NO_x are unlikely to yield measurable direct health benefits except in southern California.

NO_x, however, plays a role in the chemistry by which atmospheric ozone (O_3) is formed from reactive hydrocarbons. Ozone is a criteria pollutant because it has the potential to cause respiratory effects. [U.S. Environmental Protection Agency, Review of the National Ambient Air Quality Standards for Ozone: Assessment of Scientific and Technical Information (draft Nov. 1988) 7-1]. Much of the country, however, violates the health-based primary national ambient air quality standard for ozone. An estimated 88.6 million Americans in 1987 lived in counties that violated the ambient air quality standard for ozone. Air Quality Trends at 90. One possible mechanism for solving the very difficult problem of bringing the country into attainment of the ozone standard is reduction of NO_x emissions. See S1630, Sec. 103 (as passed by the House of Representatives.) This approach is mandated, for example, in legislation now pending before Congress. Thus, the lower NO_x emissions from automobiles that would follow use of MMT in gasoline would diminish the public health threat now resulting from widespread violation of standards for ambient levels of ozone.

Hydrocarbons (HC): Data from Ethyl Corporation's test program indicate that HC levels may increase slightly, 0.018 gm/mile. Ethyl believes, however, this increase will not occur in commercial operation because of the lower aromatic content of gasoline made possible by use of the fuel additive. Because MMT increases the octane quality of gasoline, the refiner can reformulate gasoline by removing high-octane components, such as heavy aromatics, otherwise required to meet the octane quality specification. Thus, no net increase in HC emissions should be expected. Ethyl's data also show, however, that use of the additive will result in a less reactive mix of HC. That is, it will reduce emissions of those HCs that contribute to ozone formation. Together with the substantial NO_x reductions noted above, this will decrease ambient ozone levels and diminish the

health risk attributable to exposure to ozone levels exceeding the ambient standard.

Carbon Monoxide (CO): Reductions of CO will be even more substantial than those for NO_x. Approximately 60-70% of CO in the ambient air results from passenger car emissions. The observed 0.28 gm/mile decrease in CO emissions represents approximately a 7% reduction. This figure is confirmed by data from Ethyl's 75,000 mile fleet test program, where automotive CO emissions were reduced by 7.7%.

In total, CO emissions in the U.S. would be reduced by up to 985 million pounds per year. Considering reductions in CO which would be gained at refineries would bring the total savings in CO emissions to 988 million pounds per year.

It has been well established in the literature that even small exposures to CO could result in adverse health effects. For example, Stern et al. (1988) have shown that individuals working in tunnels have higher incidence of heart disease than do their relatives who work on bridges. In addition, numerous investigators have found that individuals with heart conditions, angina, or respiratory conditions are unable to maintain their level of physical activity under exposure to CO. Therefore, EPA has established health-based primary national ambient air quality standards for CO. [Review of the National Ambient Air Quality Standards for Carbon Monoxide 50 Fed. Reg. 37484 (1985)].

Unfortunately, much of the country violates the CO standard, placing residents at an unacceptable risk of health effects. In 1987, an estimated 29.4 million Americans lived in counties that violated the primary ambient air quality standards for CO. Air Quality Trends at 90. Reductions of CO as a result of MMT use would help to alleviate this risk.

Benzene and Formaldehyde: The use of MMT as a fuel additive will decrease the average aromatic content of U.S. unleaded gasoline from 31.2% to 30.0% of the volume. This will reduce the amount of aromatics, such as benzene in tailpipe emissions.

health risk attributable to exposure to ozone levels exceeding the ambient standard.

Carbon Monoxide (CO): Reductions of CO will be even more substantial than those for NO_x. Approximately 60-70% of CO in the ambient air results from passenger car emissions. The observed 0.28 gm/mile decrease in CO emissions represents approximately a 7% reduction. This figure is confirmed by data from Ethyl's 75,000 mile fleet test program, where automotive CO emissions were reduced by 7.7%.

In total, CO emissions in the U.S. would be reduced by up to 985 million pounds per year. Considering reductions in CO which would be gained at refineries would bring the total savings in CO emissions to 988 million pounds per year.

It has been well established in the literature that even small exposures to CO could result in adverse health effects. For example, Stern et al. (1988) have shown that individuals working in tunnels have higher incidence of heart disease than do their relatives who work on bridges. In addition, numerous investigators have found that individuals with heart conditions, angina, or respiratory conditions are unable to maintain their level of physical activity under exposure to CO. Therefore, EPA has established health-based primary national ambient air quality standards for CO. [Review of the National Ambient Air Quality Standards for Carbon Monoxide 50 Fed. Reg. 37484 (1985)].

Unfortunately, much of the country violates the CO standard, [In 1987, an estimated 29.4 million Americans lived in counties that violated the primary ambient air quality standards for CO. Air Quality Trends at 90.] placing residents at an unacceptable risk of health effects. Reductions of CO as a result of MMT use would help to alleviate this risk.

Benzene and Formaldehyde: The use of MMT as a fuel additive will decrease the average aromatic content of U.S. unleaded gasoline from 31.2% to 30.0% of the volume. This will reduce the amount of aromatics, such as benzene in tailpipe emissions.

Other toxics such as formaldehyde and butadiene emitted in automobile exhaust will also be reduced. Ethyl Corporation estimates a 0.01 gm/mile reduction in total aromatics, which includes a 0.001 gm/mile reduction in benzene. A 0.001 gm/mile reduction in formaldehyde is also anticipated.

Because these pollutants may cause or contribute to adverse human health effects, reduction of their presence in automobile exhaust is a specific goal of legislation currently pending before Congress. See Senate Bill S1630 Sec. 207 (as passed by the House of Representatives). Indeed, benzene has been classified by the EPA as a human carcinogen, and several studies have shown an increased risk of leukemia due to occupational exposures (Rinsky et al., 1981; Ott et al., 1978; Wong et al., 1983). Formaldehyde has been classified by the EPA as a probable human carcinogen based on limited evidence in humans and sufficient evidence in animals (Integrated Risk Information System, EPA 1990).

The reduction in these possible carcinogens estimated by Ethyl to result from MMT use is approximately 3.5 million pounds in the U.S. for 1999. Given the nature of these substances and the possibility that even minute exposures to a carcinogen may increase the risk of cancer, it is possible that these reductions will lead to reduced numbers of cancers, particularly in highly exposed individuals.

Summary

The addition of MMT to gasoline will result in substantially reduced levels of pollution, both from tailpipe emissions and from refineries. Large reductions would be made in NO_x and CO from tailpipe emissions, and both automobiles and refineries would emit lesser quantities of aromatics such as benzene and formaldehyde. In all, reductions in refinery and tailpipe emissions will amount to approximately 1.7 billion pounds per year by 1999.

There is evidence that many of these pollutants contribute to health effects in persons exposed, and particularly in sensitive individuals. Reductions in these emissions will help prevent the occurrence of health effects, both for annoyances (ex. coughing and wheezing) as well as serious health effects (ex. heart disease and cancer).

F. SUMMARY AND CONCLUSIONS

This report examines comments from the EPA docket and evaluates the possible public health impact of the manganese emissions that would result if Ethyl's application for a waiver for MMT is granted. Our assessments mainly consisted of reviewing the toxicological and epidemiological literature on manganese. Our evaluation of health studies was based on factors such as the design of experiments, the quality of the data, sample size of studies, statistical methods used to analyze data, and conclusions drawn from statistical analyses. In some cases, attempts were made to replicate some statistical calculations. As part of our assessment of the health literature, we also considered the findings of EPA and the Health Effects Institute, two organizations that have conducted extensive reviews of the manganese literature. We also considered reviews of manganese health effects published in peer-reviewed literature.

In addition to evaluating the health literature, we also qualitatively estimated the benefits associated with using the Ethyl fuel additive. Ethyl has estimated that the use of their product would substantially reduce emissions of CO, NO_x, and aromatic hydrocarbons such as benzene. Some of these substances have been shown to be closely associated with respiratory and cardiac conditions while others are known carcinogens. Thus, the benefits derived from reducing their emissions can be substantial.

In conclusion, we have found that the use of MMT is unlikely to affect public health adversely. The anticipated increase of manganese in the environment from use of MMT is sufficiently small in comparison to the natural levels of this element and human intake of it that the body's ability to maintain consistent manganese levels should be unaffected. In fact, manganese in small quantities is an essential nutrient. Thus, no adverse effect on health would be anticipated. Data concerning the impact of exposure to the quantity of airborne manganese expected to results from use of MMT is limited, but it is consistent with this conclusion.

In general, there are only two epidemiological studies that reported effects closest to ambient levels of manganese: Gottschalk et al. (undated) and Nogawa et al. (1973). Gottschalk et al. found an association between hair levels of manganese and violent behavior, but these findings are suspect because the study was poorly designed. There is strong evidence that hair levels of manganese do not accurately reflect body levels, and the study failed to consider key critical social factors. In addition, it does not link the hair manganese levels to inhaled manganese and does not indicate a causal role for manganese in violence. The only other study that showed respiratory effects in humans at near ambient levels of manganese is Nogawa et al. (1973). As the HEI report correctly points out, this study suffered from substantial limitations, and it is almost impossible to determine at what levels respiratory effects occurred. In any event, the estimated manganese levels in Nogawa are still well above those that would follow addition of MMT to gasoline.

Finally, we have found that none of the three major issues raised by commenters on the Ethyl application is of concern. First, manganese is very different from lead chemically, biologically, and environmentally. Thus, the experience with lead as a gasoline additive cannot be used as a model of what will happen if MMT is added to gasoline. Second, while high levels of manganese (i.e. >300 $\mu g/m^3$) are associated with neurological effects, concern that exposure to the far lower manganese levels expected to results from MMT use (e.g. 0.034 to 0.12 $\mu g/m^3$) has no basis. Finally, the concern that manganese is associated with violent criminal behavior is essentially speculation. The one study that directly supports it is seriously flawed. Similarly, none of the other concerns raised by commenters provide a sound basis for concluding that the addition of MMT to gasoline as proposed by Ethyl would endanger public health.

G. REFERENCES

Abbott, P.J. (1987) *Methylcyclopentadienyl Manganese Tricarbonyl (MMT) in Petrol: The Toxicological Issues.* Sci. Total Environ. 67:247-255.

Barbeau, A. (1984) *Manganese and Extrapyramidal Disorders.* Neurotoxicology 5(1):13-36.

Bleecker, M.L. (1988) *Parkinsonism: A Clinical Marker of Exposure to Neurotoxins.* Neurotoxicol. Teratol. 10(5):475-478.

Cawte, J. (1984) *Emic Accounts of a Mystery Illness: The Groote Eylandt Syndrome.* Aust. N. Z. J. Psychiatry 18:179-187.

Cawte, J.; Kilburn, C.; Florence, M. (1989) *Motor Neurone Disease of the Western Pacific: Do the Foci Extend to Australia?* Neurotoxicology 10:263-270.

Cooper, W.C. (1984) *The Health Implications of Increased Manganese in the Environment Resulting From the Combustion of Fuel Additives.* J. Toxicol. Environ. Health 14:23-46.

Davis, D.W.; Hsiao, K.; Ingels, R.; Shikiya, J. (1988) *Origins of Manganese in Air Particulates in California.* J. Air Pollut. Control Assoc. 38(9):1152-1157.

Donaldson, J.; LaBella, F.S.; Gesser, D. (1980) *Enhanced Autoxidation of Dopamine as a Possible Basis of Manganese Neurotoxicity.* Neurotoxicology 2:53-64.

Donaldson, J. (1987) *The Physiopathologic Significance of Manganese in Brain: Its Relation to Schizophrenia and Neurodegenerative Disorders.* Neurotoxicology 8(3):451-462.

Donaldson, J. (1988) *Manganese and Human Health.* In: Manganese in the Canadian Environment. Associate Committee on Scientific Criteria for Environmental Quality, National Research Council Canada, NRCC no. 26193.

Gottschalk, L.A.; Rebello, T.; Buchsbaum, M.S.; Tucker, H.G.; Hodges, E.L. (undated) *Manganese, a Physiological Marker for Criminal Violence*. Unpublished.

Hams, G.A.; Fabri, J.K. (1988) *An Analysis for Blood Manganese Used to Assess Environmental Exposure*. Clin. Chem. 34(6):1121-1123.

Health Effects Institute (1988) *Potential Health Effects of Manganese in Emissions From Trap-Equipped Diesel Vehicles*. Cambridge, MA.

Huang, C.C.; Chu N.S.; Lu C.S.; Wang, J.D.; Tsai,J.L.; Tzeng, J.L.; Wolters, E.K.; Calne, D.B. (1989) *Chronic Manganese Intoxication*. Arch. Neurol. 46:1104-1106.

Joselow, M.M.; Tobias, E.; Koehler, R.; Coleman, S.; Bogden, J.; Gause, D. (1978) *Manganese Pollution in the City Environment and Its Relationship to Traffic Density*. Am. J. Public Health 68:557-560.

Maugh, T.H. (1978) *Hair: A Diagnostic Tool to Complement Blood Serum and Urine*. In: Science 202:1271-1273.

Mena, I.; Marin, O.; Fuenzalida, S.; Cotzias, G.C. (1967) *Chronic Manganese Poisoning: Clinical Picture and Manganese Turnover*. Neurology 17:128-136.

National Institutes of Environmental Health Sciences, Director (1990) Memorandum to Deputy Administrator for Pesticides and Toxic Substances, EPA. Research Triangle Park, NC.

Needleman, H.L. (1990) Letter to U.S. EPA Air Docket LE 131. Pittsburgh, PA: University of Pittsburgh, Western Psychiatric Institute and Clinic.

Nogawa, K.; Kobayashi, E.; Sakamoto, M.; Fukushima, N.; Ishizaki, A.; Makino, N.; Kagamimori, S.; Hiramaru, Y.; Kawano, S.; Kato, T.; Kanekawa, K.; Shozo. (1973) *Studies of the Effects on the Respiratory Organs of Air Pollution Consisting of Dusts Composed Mainly of Manganese. (First Report) Effects on the Respiratory Organs of Junior High School Students*. Japan J. Public Health 20(6):315-325.

Ott, M.G.; Townsend, J.C.; Fishbeck, W.A.; Langner, R.A. (1978) *Mortality Among Individuals Occupationally Exposed to Benzene.* Arch. Environ. Health 33(1):3-10.

Phoon, W.H. (1988) *Manganese Exposure and Biological Indicators.* Sing. Med. J. 29:93-94.

Rinsky, R.A.; Young, R.J.; Smith, A.B. (1981) *Leukemia in Benzene Workers.* Am. J. Ind. Med. 2(3):217-245.

Roels, H.; Lauwerys, R.; Buchet, J.P.; Genet, P.; Sarhan, M.J.; Hanotiau, I.; de Fays, M.; Bernard, A.; Stanescu, D. (1987) *Epidemiological Survey Among Workers Exposed to Manganese: Effects on Lung, Central Nervous System, and Some Biological Indices.* Am. J. Ind. Med. 11:307-327.

Roels, H.; Lauwerys, R.; Genet, P.; Sarhan, M.J.; de Fays, M.; Hanotiau, I.; Buchet, J.P. (1987) *Relationship Between External and Internal Parameters of Exposure to Manganese in Workers From a Manganese Oxide and Salt Producing Plant.* Am. J. Ind. Med. 11:297-305.

Griffin, H.E. (1984) Letter to William D. Ruckelshaus, EPA Administrator, Washington, DC.

Saric, M.; Markicevic, A.; Hrustic, O. (1977) *Occupational Exposure to Manganese.* Br. J. Ind. Med. 34:114-118.

Sky-Peck, H.H. (1990) *Distribution of Trace Elements in Human Hair.* Clin. Physiol. Biochem. 8:70-80.

Smyth, L.T.; Ruhf, R.C; Whitman, N.E.; Dugan, T. (1973) *Clinical Manganism and Exposure to Manganese in the Production and Processing of Ferromanganese Alloy.* J. Occup. Med. 15(2):101-109.

Stauber, J.L.; Florence, T.M. (1989) *Manganese in Scalp Hair: Problems of Exogenous Manganese and Implications for Manganese Monitoring in Groote Eylandt Aborigines.* Sci. Total Environ. 83:85-98.

Stern, F.B.; Halperin, W.E.; Hornung, R.W.; Ringenburg, V.L.; McCammon, C.S. (1988) *Heart Disease Mortality Among Bridge and Tunnel Officers Exposed to Carbon Monoxide.* Am. J. Epidemiol. 128:1276-1288.

Ulrich, C.E.; Rinehart, W.; Busey, W. (1979) *Evaluation of the Chronic Inhalation Toxicity of a Manganese Oxide Aerosol. I. Introduction, Experimental Design and Aerosol Generation Methods.* Am. Ind. Hyg. Assoc. J. 40:238-244.

Ulrich, C.E.; Rinehart, W.; Busey, W.; Durato, M.A. (1979) *Evaluation of the Chronic Inhalation Toxicity of a Manganese Oxide Aerosol. II. Clinical Observations, Hematology, Clinical Chemistry, and Histopathology.* Am. Ind. Hyg. Assoc. J. 40:322-329.

Ulrich, C.E.; Rinehart, W.; Brandt, M. (1979) *Evaluation of the Chronic Inhalation Toxicity of a Manganese Oxide Aerosol. III. Pulmonary Function, Electromyograms, Limb Tremor, and Tissue Manganese Data.* Am. Ind. Hyg. Assoc. J. 40:349-353.

U.S. Environmental Protection Agency. (1984) *Health Assessment Document for Manganese.* Cincinnati, OH: Environmental Criteria and Assessments Office, Office of Research and Development, EPA report no. EPA-600/8-83-013F.

U.S. Environmental Protection Agency. (1985) *Review of the National Ambient Air Quality Standards for Carbon Monoxide.* 50 Federal Register 37484.

U.S. Environmental Protection Agency. (1988) *Review of the National Ambient Air Quality Standard for Ozone: Assessment of Scientific and Technical Information (Draft).*

U.S. Environmental Protection Agency. (1989) *National Air Quality and Emissions Trends Report, 1987.* EPA report no. EPA 450/4-89-001.

U.S. Environmental Protection Agency. (1990) *Air Quality Criteria for Carbon Monoxide (Draft).* Research Triangle Park, NC: Office of Health and Environmental Assessment, Office of Research and Development, EPA report no. EPA/600/8-90/045A.

U.S. Environmental Protection Agency. (1990) Integrated Risk Information System (IRIS).

Wang, J.D.; Huang, C.C.; Hwang, Y.H.; Chiang, J.R.; Lin, J.M.; Chen, J.S. (1989) *Manganese Induced Parkinsonism: An Outbreak Due to an Unrepaired Ventilation Control System in a Ferromanganese Smelter.* Br. J. Ind. Med. 46:856-859.

ATTACHMENT A-1

Curriculum Vitae for Drs. Higgins, Landau,
Roth, and Schulz, and Mr. Walker

CURRICULUM VITAE

NAME	HIGGINS, IAN THOMAS TWISTINGTON
CITIZENSHIP	United States
PLACE AND DATE OF BIRTH	Edinburgh, Scotland March 12, 1919
EARLY EDUCATION	Gresham's School, Holt, Norfolk
MEDICAL SCHOOL	London Hospital
STATUS	Married, two children

ACADEMIC QUALIFICATIONS

M.R.C.S., L.R.C.P.	1942 (London)
M.R.C.P.	1945 (London)
M.B., B.S.	1946 (London)
M.D.	1951 (London)
F.R.C.P.	1972 (London)

ACADEMIC DISTINCTIONS

Charrington Prize in Anatomy

Arnold Thompson Prize in Diseases of Children

Adolph G. Kammer Merit in Authorship Award of Industrial Medical Association. 1969.

PRESENT APPOINTMENT

Professor of Epidemiology and Professor of Environmental and Industrial Health, School of Public Health, University of Michigan, Ann Arbor, Michigan. 1970 to present.

PAST APPOINTMENTS

Professor of Epidemiology and Professor of Community Health Services, Director of the Chronic Disease, Adult Health and Aging Unit, School of Public Health, University of Michigan.	1966-1970
Professor Chronic Disease Epidemiology, Graduate School of Public Health, University of Pittsburgh.	1963-1966

IAN T. T. HIGGINS

PAST APPOINTMENTS (continued)

Assistant Director of Medical Research, Council's Epidemiological Research Unit, Cardiff, United Kingdom.	1962-1963
Member of the Scientific Staff of the Medical Research Council's Pneumoconiosis Research Unit, Cardiff, United Kingdom.	1953-1962
Hospital Appointments in General Medicine, Pediatrics and Diseases of the Chest in various hospitals in the United Kingdom.	1943-1953

COMMITTEES

UNIVERSITY

Senate Assembly	1971-1974

STATE

Committee on Screening and Risk Reduction of Michigan Heart Association	1971-1975

NATIONAL

National Academy of Sciences/National Research Council

Committee on Biological Effects of Environmental Pollutants: Chairman of Panel on Effects of Airborne Particles.	1972-1975
Committee on Research Needs on the Health Effects of Fossil Fuel Combustion Products	1976-present
Committee on Toxicology	1977-present
Subcommittee on Herbicide Orange in the Vietnam war	1979
Food Safety and Food Safety Policy Panel 1 Saccarin and Risk - Benefit Assessment	1977-present
Subcommittee on Safe Drinking Water	1977-1978
Committee on Diesel Emissions	1978-present

IAN T. T. HIGGINS

American Heart Association	
Program Committee	1969-1974
National Institute of Environmental Health Sciences	
Program Committee of Second Task Force for Research	1976
Environmental Protection Agency	
Task Group for Health Effects Studies	1975-present
National Heart Lung and Blood Institute	
Task Force on Standardization for Epidemiological Surveys. Reports on: 1) Environmental Factors and 2) Occupational Factors in Chronic Respiratory Diseases	1974
American Lung Association	
Committee on Smoking Cessation	1976-present
American Thoracic Society	
Committee on Research	1972-1974
Committee on Occupational and Environmental Health	1972-present
Chairman: Nomination Committee, Scientific Assembly on Occupational and Environmental Health	1975

IAN T.T. HIGGINS

PAST MEMBER OF

National Advisory Committee on Air Quality Criteria, United States Public Health Service.	1967-1970
Air Pollution Training Grants and Fellowships Committee, United States Public Health Service.	1966-1969
Task Force on Research Planning in Environmental Health Science; Co-Chairman of Subcommittee on Epidemiology and Air Pollution.	1969
National Cancer Institute Tobacco Working Group	1974-1977

LEARNED SOCIETIES

United Kingdom

Fellow of the Royal Society of Medicine.
Member of the British Thoracic and Tuberculosis Society.
Associate Member of the Thoracic Society.
Member of the Society for Social Medicine.

United States

Member of the American Epidemiological Society.
Fellow of the Council on Arteriosclerosis of the American Heart Association.
Member of the Association of Teachers of Preventive Medicine.
Member and Counsellor at Large of the Society for Occupational and Environmental Health.

OTHER ACTIVITIES

Consultant to Aerosol Safety Subcommittee of the Cosmetics, Toiletries and Fragrance Association.
Member of the Scientific Committee of the Institute of Occupational and Environmental Health of the Quebec Asbestos Mining Association.
Consultant to National Cancer Institute on Exposure to Chemical Carcinogens and Recommended Control.
Editorial Consultant or member for the Journal of Chronic Diseases, American Journal of Epidemiology, American Review of Respiratory Diseases, Archives of Environmental Health.
* Member of the Committee on Toxicology, National Academy of Sciences, 1977 to present.
* Member of the Food Safety and Food Safety Policy Panel I - Saccharin and Risk - Benefit Assesstment, National Academy of Sciences, 1977 to present.

IAN T.T. HIGGINS

OTHER ACTIVITIES (continued)

* Member of the Committee on Research Needs on the Health Effects of Fossil Fuel Combustion Products, National Research Council, 1976 to present.
* Member of the Subcommittee on Epidemiology of Safe Drinking Water Committee, National Academy of Sciences, 1977 to 1978.
* Member of the Epidemiological Task Group for Health Effects Studies, Environmental Protection Agency, 1975 to present.

Member of the Committee on Smoking Cessation, American Lung Association, 1976 to present.

National Heart, Lung and Blood Institute Task Force reports on: 1) Environmental factors, and 2) Occupational factors in chronic respiratory diseases.

* Particularly relevant

Ian T. T. Higgins

PUBLICATIONS

1. Higgins, I.T.T. Spontaneous pneumothorax in the newborn. Arch. Dis. Children, 1945.

2. Cotes, J.E., Higgins, I.T.T. and Thomas, A.J. Relationship of coronary heart diseases to respiratory disability. Brit. Med. J. i:601, 1956.

3. Higgins, I.T.T., Oldham, P.D., Merrick, A.J. and Dunsdon, M.I. Selection of Miners: A survey of school-leavers in a valley in South Wales. Brit. J. Soc. Med. 10:32, 1956.

4. Thomas, A.J., Cotes, J.B. and Higgins, I.T.T. Prevalence of coronary heart disease in elderly coal workers. Lancet i:414, 1956.

5. Carpenter, R.G., Cochrane, A.L., Gilson, J.C. and Higgins, I.T.T. The relationship between ventilatory capacity and simple pneumoconiosis in coal workers: The effect of population selection. Brit. J. Indus. Med. 13:166, 1956.

6. Higgins, I.T.T., Cochrane, A.L., Oldham, P.D. and Gilson, J.C. Respiratory symptoms and pulmonary disability in an industrial town. Brit. Med. J. ii:904, 1956.

7. Higgins, I.T.T. Tuberculosis and progressive massive fibrosis: Illustrative cases occurring in one family. Tubercle. 38:123, 1957.

8. Higgins, I.T.T. Respiratory symptoms, bronchitis and ventilatory capacity in a random sample of an agricultural population. Brit. Med. J. ii:540, 1958.

9. Thomas, A.J., Cochrane, A.L. and Higgins, I.T.T. The measurement of the prevalence of ischaemic heart disease. Lancet ii:540, 1958.

10. Higgins, I.T.T. and Cochrane, A.L. Respiratory symptoms, bronchitis and disability in a random sample of an agricultural community in Dumfrieshire. Tubercle. 39:399, 1958.

11. Cochrane, A.L., Higgins, I.T.T. and Gilson, J.C. Yet another industrial pneumoconiosis? Tubercle. 39:399, 1958.

12. Higgins, I.T.T. Tobacco smoking, respiratory symptoms and ventilatory capacity: Studies in random samples of the population. Brit. Med. J. i:325, 1959.

13. Higgins, I.T.T., Cochrane, A.L., Gilson, J.C. and Wood, C.N. Population studies of chronic respiratory disease. A comparison of miners, foundry workers, and others in Staveley, Derbyshire. Brit. J. Indus. Med. 16: 185 and 255, 1959.

PUBLICATIONS (continued)

14. Higgins, I.T.T. An approach to the problem on bronchitis in industry. Studies in agricultural, mining and foundry communities. Symposium on Industrial Pulmonary Diseases, ed. by E.J. King and D.N. Fletcher. Chapter 16, pp.195-207. J. and A. Churchill, Ltd., London, 1960.

15. Cochrane, A.L., Higgins, I.T.T. and Thomas, J. Pulmonary ventilatory functions of coal miners in various areas in relation to the x-ray category of pneumoconiosis. Brit. J. Soc. Prev. Med. 15:1-11, 1961.

16. Higgins, I.T.T. and Cochrane, A.L. Chronic respiratory disease in a random sample of men and women in Rhondda Fach in 1958. Brit. J. Indus. Med. 18:93, 1961.

17. Higgins, I.T.T. and Oldham, P.D. Ventilatory capacity in miners: A five year follow-up study. Brit. J. Indus. Med. 19:65, 1962.

18. Hart, J.T., Cochrane, A.L. and Higgins, I.T.T. Tuberculin sensitivity in coal workers' penumoconiosis. Tubercle. 44:141, 1962.

19. Higgins, I.T.T., Thomas, A.J. and Cochrane, A.L. Epidemiological studies of coronary disease. Brit. J. Prev. Med. 17:153-165, 1963.

20. Higgins, I.T.T., Oldham, P.D., Kikpatrick, G.S., Drummond, R.J. and Bevan, B. Blood groups of miners with pneumoconiosis and bronchitis. Brit. J. Indus. Med. 20:324, 1963.

21. Higgins, I.T.T. and Oldham, P.D. Tobacco smoking and blood group. Brit. Med. J. 2:1167, 1963.

22. Higgins, I.T.T. Smoking. Aging of the Lung, ed. by Leon Cander, pp.227-238. Grune and Stratton, New York City, 1964.

23. Higgins, I.T.T. Length of cigarette ends and inhaling. Brit. J. Indus. Med. 21:321, 1964.

24. Higgins, I.T.T. International comparability in epidemiological studies. I. Ischaemic heart disease. The problem. Milbank Mem. Fund Quart. 43: 23, 1965.

25. Higgins, I.T.T., Kannel, W.B. and Dawber, T.R. The electrocardiogram in epidemiological studies. Brit. J. Prev. Soc. Med. 19:53, 1965.

26. Higgins, I.T.T. The epidemiology of congenital heart disease. J. Chron. Dis. 18:699-721, 1965.

27. Cotes, J.E., Rossiter, C.E., Higgins, I.T.T. and Gilson, J.C. Average normal values for the forced expiratory volume in white Caucasian males. Brit. Med. J. 1:1016-19, 1966.

PUBLICATIONS (continued)

28. Higgins, I.T.T. Air pollution and chronic respiratory disease. ASHRAE J. August, 1966, pp.37-46.

29. Lockshin, M.D. and Higgins, I.T.T. Bone metastases in osteogenic sarcoma. Arch. Intern. Med. 118, September, 1966.

30. Higgins, I.T.T., Higgins, M.W., Lockshin, M.D. and Canale, N. Chronic respiratory disease in mining communities in Marion County, West Virginia. Brit. J. Indus. Med. 25:165, 1968.

31. Higgins, I.T.T. Beryllium Poisoning. Medical Times. 96:25, 1968.

32. Lockshin, M.D. and Higgins, I.T.T. Prognosis in osteogenic sarcoma. Clin. Orth. Related Research. 58, 1968.

33. Higgins, I.T.T., Gilson, J.C., Ferris, B.G., Waters, M.B., Campbell, H. and Higgins, M.W. Chronic respiratory disease in an industrial town: A nine year follow-up study. Preliminary report. Amer. J. Pub. Hlth. 58: 1667, 1968.

34. Higgins, I.T.T., Higgins, M.W., Lockshin, M.D. and Canale, N. Coronary disease in mining communities in Marion County, West Virginia. J. Chron. Dis. 22:165, 1969.

35. Lockshin, M.D., Higgins, I.T.T., Higgins, M.W., Dodge, H.J. and Canale, N. Rheumatism in mining communities in Marion County, West Virginia. Am. J. Epid. 90:17, 1969.

36. Higgins, I.T.T. and McCarroll, J.R. Types, ranges and methods for classifying human pathophysiologic changes and responses to air pollution. In Development of Air Quality Standards, ed. by Arthur Atkinson and Richard S. Gaines. 1969.

37. Higgins, I.T.T. Occupational factors in chronic nonspecific lung disease in Bronchitis III. Third International Symposium, ed. by N.G.M. Orie and R. VanDerLunde. Royal VanGorcum, Assen, The Netherlands, 1970.

38. Higgins, I.T.T. Medical Aspects of Air Pollution: Sulphur Oxides and Particulates. Society of Automotive Engineers, Inc. Proceedings of a Symposium held in Detroit, Michigan, on January 14, 1971.

39. Higgins, I.T.T. Effects of Sulphur Oxides and Particulates on Health. Arch. Env. Hlth. 22:584-590, 1971.

40. Ferris, B.G., Higgins, I.T.T., Higgins, M.W., Peters, J.M., VanGanse, W.F. and Goldman, M.D. Chronic nonspecific respiratory disease, Berlin, New Hampshire, 1961-1967: A cross-sectional study. Amer. Rev. Resp. Dis. 104:232-244, 1971.

PUBLICATIONS (continued)

41 Higgins, I.T.T., Higgins, M.W., Gilson, J.C., Campbell, H. Waters, W.E. and Ferris, B.G. Smoking and chronic respiratory disease: Findings in surveys carried out in 1957 and 1966 in Staveley in Derbyshire, England. Chest 59:34-35S, 1971.

42. Higgins, I.T.T. Recent mortality from cancer of the cervix in the United States and United Kingdom. Lancet 2:1141-1143, 1971.

43. Higgins, I.T.T. Recent developments in the epidemiology of chronic non-specific lung disease (CNSLD). Cara-Symposium, The Netherlands Astma fond. pp.9-26, Assen 1972.

44. Higgins, I.T.T., Lockshin, M.D., Gilson, J.C., Cochrane, A.L., Campbell, H., Waters, W.E., Ferris, B.G., Jr., Oh, M. and Higgins, M.W. Coronary disease in Staveley, Derbyshire with an international comparison with three towns in Marion County, West Virginia. J. Chron. Dis. 25:567-580, 1972.

45. Higgins, I.T.T. Epidemiological approaches to the study of sub-clinical effects of mercury intoxication in Environmental Mercury Contamination by R. Hartung and B.D. Dinman. pp.331-341, 1972.

46. Higgins, I.T.T. Chronic respiratory disease in mining communities. Annals of the New York Academy of Sciences 200:197-210, 1972.

47. Ferris, B.G., Jr., Higgins, I.T.T., Higgins, M.W. and Peters, J.M. Chronic non-specific respiratory disease, Berlin, New Hampshire, 1961-1967: A follow-up study. Amer. Rev. Resp. Dis. 107:110-122, 1973.

48. Higgins, I.T.T. Epidemiology of chronic respiratory disease. Preventive Medicine 2:14-33, 1973.

49. Ferris, B.G., Jr., Higgins, I.T.T., Higgins, M.W. and Peters, J.M. Sulphur oxides and suspended particulates. Arch. Env. Health 27:179, 1973.

50. Higgins, I.T.T. and Ferris, B.G., Jr. Proceedings of the Conference on Health Effects of Air Pollutants. Assembly of Life Sciences. NSA S.N.R.C. Committee on Public Works, U.S. Govt. Printing Office, Washington, D.C., 1973.

51. I.T.T. Higgins. Health effects of sulphur oxides: Background review: Epidemiology. Environmental Health Perspectives 8:115, 1974.

52. Carpenter, J.O., McArthur, R.F. and Higgins, I.T.T. The aged: Health, illness, disability and use of medical services. Chapter in the APHA Monograph. Harvard University Press, Cambridge, 1974.

53. Higgins, I.T.T. Trends in mortality from cancer of the respiratory system in the United States and England and Wales. Arch. Env. Hlth. 28:121, 1974.

PUBLICATIONS (continued)

54. Higgins, I.T.T. Review of trends in epidemiology: Application to health service research and training. Edited by Gordon T. Stewart. J. Chron. Dis. 27:172, 1974.

55. Higgins, I.T.T. Epidemiology of chronic respiratory disease: A literature review prepared for the Office of Research and Development, Environmental Protection Agency, Washington, D.C. 20460, August, 1974.

56. Higgins, I.T.T. Critical review of respiratory therapy: Epidemiological considerations. Amer. Rev. Resp. Dis. 110:16-19, 1974.

57. Higgins, I.T.T. Epidemiology of cancer of the prostate. J. Chron. Dis. 28:343-348, 1975.

58. Higgins, I.T.T. Importance of epidmeiological studies relating to hazards of food and environment. Brit. Med. Bull. 31:230-235, 1975.

59. Higgins, I.T.T. Relative risks of various tobacco usages for emphysema and/or chronic bronchitis. Paper presented at the Third World Conference on Smoking and Health, 1975. Proceedings/3rd World Conference, Smoking and Health, Vol. 1, pp. 389-405, 1976.

60. Higgins, I.T.T. Smoking and cancer of the lung. Amer. J. Publ. Hlth. 66:159-161, 1976.

61. Higgins, I.T.T. Cancer of the lung in the United States. IARC Scientific Publications, No. 16, pp. 191-203, 1977.

62. Higgins, I.T.T. Epidemiological Evidence on the Carcinogenic risk of air pollution. In Environmental Pollution and Carcinogenic Risks Inserm, 52:41-52, 1976.

63. Higgins, I.T.T., Albert, R.E., Charlson, R.J., Darley, E.F., Ferris, B.G., Jr., Frank, R and Whitby, K.T. Airborne Particles. National Academy of Sciences, Washington, D.C. 1977. (553 pages)

64. Garn, S.M., Bailey, S.M. and Higgins, I.T.T. Fatness similarities in adopted pairs. Am. J. Clin. Nutr. 29:1067-1068, 1976.

65. Garn, S.M., Bailey S.M., Cole, P.E. and Higgins, I.T.T. Level of education level of income and level of fatness in adults. Am. J. Clin. Nutr. 30: 721-725, 1977.

66. Garn, S., Bailey, S., Cole, P. and Higgins, I.T.T. Evidence for the social inheritance of obesity in childhood and adolescence. In: L. Gedda and P. Parisi, Ed., Auxology: Human Growth in Health and Disorder. Proceedings of the Serono Symposium, Academic Press, 1978.

67. Higgins, I.T.T. Epidemiology of bronchitis and emphysema. Chapter 36, 470-475 in Pulmonary Diseases and Disorders, Editors, Fishman, A.P. and McGraw-Hill, 1979.

PUBLICATIONS (continued)

68. Higgins, I., Lilienfeld, A.M., Last, J.M. Ill Effects of Tobacco Smoking. In: Public Health and Preventive Medicine. Chapter 27. 11th Edition. Maxcy-Rosenau. Editor, J.M. Last. Appleton-Century Crofts, New York, 1980.

69. Higgins, I. Respiratory Disease. Chapter 36. ibid, 1981.

70. Higgins, I. Arsenic Health Effects. pp. 4-127 to 4-148. In Environmental Impact Statement for ASARCO. March 1981.

71. Higgins, I.T.T., Oh M., Whittaker, D.E. Chronic Respiratory Disease in Coal Miners. Follow-up Study of Two Mining Communities in West Virginia. NIOSH Technical Report, 1981.

72. Higgins, I.T.T. Cross-Sectional Studies. Conference on Epidemiologic Methods for Occupational and Environmental Studies, Society for Occupational and Environmental Health. Washington, D.C. December 3, 1979. In Press. Environ. Hlth. Perspect.

73. Higgins, I.T.T. Asbestos in Drinking Water and Cancer Incidence in the San Francisco Bay Area. Am. J. Epid. 114:161-162, 1981.

74. Higgins, I., Welch, K., Oh, M., Bond, G., and Hurwitz, P. Influence of Arsenic Exposure and Smoking on Lung Cancer Among Smelter Workers: A Pilot Study. Am. J. Indust. Med. 2:33-41, 1981.

75. Higgins, I., Stolley, P., Wynder, E.L. Coffee and Cancer of the Pancreas. New Eng. J. Med. 304:1605, 1981.

76. Higgins, M.W., Keller, J.B., Becker, J., Howatt, W., Landis, J.R., Rotman, H., Weg, J.G. and Higgins, I. An Index of Risk for Obstructive Airways Disease. Am. Rev. Resp. Dis. 1981. (In Press)

AMERICAN PUBLIC HEALTH ASSOCIATION

Emanuel Landau
Project Coordinator

PROFESSIONAL EXPERIENCE

Emanuel Landau is an epidemiologist who has over 30 years experience in environmental health activities. He is accepted as a national authority on assessing health effects of exposure to air pollutants and other contaminants. As the Staff Epidemiologist at APHA, he provides the technical competence necessary from answering letters of inquiry to evaluating health risks.

During his tenure at APHA, Dr. Landau has served as Project Director of studies of occupational and community exposure to inorganic arsenic directed to neurological as well as carcinogenic effects. Another carcinogen, vinyl chloride, was the focus of studies in Quebec, Canada, as well as in Louisville, Kentucky. An occupational study of PBB-induced health impairments demonstrated the first instance of thyroid dysfunction reported in the scientific literature.

Some of the studies serve as illustrations of demonstrated ability to respond quickly to need. One was the resurvey of the health effects of exposure to fibrous glass emissions in an adjacent community. No adverse effects were found in the resurvey as contrasted with the original survey (not carried out by APHA). The study of a railroad spill of orthochlorophenol contaminated with dioxin demonstrated again the technical capability of APHA as well as its quick response time.

Dr. Landau has recently completed at APHA the training course on hazardous waste management for nationwide environment educators.

Prior to joining APHA, Dr. Landau served the former Department of Health, Education and Welfare in the following capacities:

- As Chief, Epidemiologic Studies Branch, Bureau of Radiological Health, Dr. Landau initiated and conducted epidemiologic research into effects of exposure to ionizing and non-ionizing radiation, both in the United States and overseas (England and Poland).

- As Epidemiologist, Office of the Assistant Administrator for Research and Development, Environmental Health Service (EHS), Dr. Landau served as the primary focal point for activities in EHS of an epidemiologic, demographic and statistical nature. EHS covered the areas of air pollution, radiation, solid waste, occupational health and safety and community management.

- As Statistical Advisor to the Associate Commissioner and Commissioner, National Air Pollution Control Administration, Dr. Landau was principal staff advisor on the statistical aspects of research activities. He served as Associate Commissioner for Standards and Criteria Development in the absence of the Associate Commissioner.

- As Head, Laboratory and Clinical Trials Section, National Cancer Institute, Dr. Landau was responsible for planning, guiding, developing and coordinating a program of clinical trials in humans and laboratory evaluations in animals.

- As Chief, Biometry Section, Division of Air Pollution, Dr. Landau planned epidemiologic studies of the effects of air pollution. As Supervisory Analytical Statistician, California State Department of Public Health (assigned by the Division of Air Pollution, U.S. Public Health Service), Dr. Landau planned and conducted research to determine effects of air pollution on health.

Other accomplishments include:

- Superior Service Award (DHEW) on health effects of air pollution; WHO Temporary Advisor on air quality criteria 1967; Advisor on Air Quality Criteria, Karolinska Institute, Stockholm, Sweden 1968; Advisor to Department of Transportation on biological effects of operating a fleet of supersonic planes 1972-74; Consultant, Bureau of Radiological Health, 1975 to present; Consultant, EPA on air quality criteria, 1980-81; Participated in site visits for AEC, ERDA, HIEHS and EPA; elected member of Cosmos Club, Washington, D.C.

LANGUAGE SKILLS

English: Native language
French: Working knowledge
Spanish: Working knowledge

CHRONOLOGICAL SUMMARY OF EMPLOYMENT

Organization	Date	Title
American Public Health Association	1975 to present	Project Director and Project Coordinator
Bureau of Radiological Health (DHEW)	1971-1974	Chief, Epidemiologic Studies Branch
Office of the Ass't. Administrator for R&D, EHS, DHEW	1969-1971	Epidemiologist
National Air Pollution Control Administration, DHEW	1964-1969	Statistical Advisor
National Cancer Institute, DHEW	1962-1964	Head, Laboratory and Clinical Trials Section
Division of Air Pollution, DHEW	1959-1962	Chief, Biometry Section
California State Dept. of Public Health (assigned from U.S. Public Health Service)	1957-1959	Supervisory Analytic Statistician